Nutrition Management of Pediatric Patients Who Have Cystic Fibrosis

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KEYWORDS

• Cystic fibrosis • Nutrition • Vitamins • Minerals • Energy • Protein • Fatty acids • Pancreatic • Enzymes

Cystic fibrosis (CF) is a common autosomal recessive genetic disorder, most often seen in people of northern European decent and in lesser frequency in other racial groups. Current US data indicate that CF occurs in approximately 1 in 2500 births and affects approximately 30,000 individuals. The gene, which is on chromosome 7, is called the CF transmembrane regulator and controls the flow of sodium and chloride ions across the cell membrane. Prior to the availability of newborn screening in the United States, the diagnosis of CF usually was not made until an infant or child developed pulmonary disease or gastrointestinal symptoms, often with failure to thrive and nutrient deficiencies. Poor weight gain and vitamin and mineral deficiencies usually are corrected with the use of pancreatic enzyme replacement therapy (PERT) and vitamin and mineral supplements.[1] Multivitamin supplements designed for infants, children, and adults who have CF are available in the United States (**Table 1**).

Pancreatic damage can start in utero, with approximately 80% of babies being pancreatic insufficient (PI) at diagnosis. Management of patients who are PI includes use of PERT. For infants, PERT is initiated at 2000 to 5000 lipase units per feeding and, as with all patients who are PI, adjusted to a maximum of 2500 lipase units per kilogram per meal not to exceed 10,000 lipase units per kilogram per day.[1] Patients who are pancreatic sufficient (PS) may go on to become PI; therefore, careful monitoring of pancreatic function is recommended, especially for those patients with

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Table 1
Comparison of cystic fibrosis–specific vitamin and mineral supplements in United States to non–cystic fibrosis-specific products[a]

Age	SourceCF[b,c] Drops, Chewables, and Softgels	ADEK Chewables[b,d]	AquADEKs[b,e] Drops and Softgels	Vitamax[b,f] Drops and Chewables	Poly-Vi-Sol Drops[g] and Centrum Chewables and Tablet
Vitamin A (IU): retinol and beta carotene					
0–12 mo	4627 (1 mL) 75% BC	—	5751 (1 mL) 87% BC	3170 (1 mL) 0% BC	1500 (1 mL) 0% BC
1–3 y	9254 (2 mL) 75% BC	—	11502 (2 mL) 87% BC	6340 (2 mL) 0% BC	3000 (2 mL) 0% BC
4–8 y	16,000/chewable 88% BC	9000/chewable 60% BC	Ages 4–10 y: 18,167/1 softgel 92% BC	5000/chewable 50% BC	3500/chewable 29% BC
>9 y	32,000/2 softgels 88% BC	18,000/2 chewables 60% BC	Ages 10 and up: 36,334/2 softgels 92% BC	10,000/2 chewables 50% BC	7000/2 tablets 29% BC
Vitamin E (IU)[h]					
0–12 mo	50 (1 mL)	—	50 (1 mL)[i]	50 (1 mL)	5 (1 mL)
1–3 y	100 (2 mL)	—	100 (2 mL)[i]	100 (2 mL)	10 (2 mL)
4–8 y	200/chewable	150/chewable	Ages 4–10 y: 150/1 softgel[i]	200/chewable	30/chewable
>9 y	400/2 softgels	300/2 chewables	Ages 10 and up: 300/2 softgels[i]	400/2 chewables	60/2 tablets
Vitamin D (IU)					
0–12 mo	500 (1 mL)	—	400 (1 mL)	400 (1 mL)	400 (1 mL)
1–3 y	1000 (2 mL)	—	800 (2 mL)	800 (2 mL)	800 (2 mL)
4–8 y	1000/chewable	400/chewable	Ages 4–10 y: 800/1 softgel	400/chewable	400/chewable
>9 y	2000/2 softgels	800/2 chewables	Ages 10 and up: 1600/2 softgels	800/2 chewables	800/2 tablets

Vitamin K (μg)					
0–12 mo	400 (1 mL)	—	400 (1 mL)	300 (1 mL)	0
1–3 y	800 (2 mL)	—	800 (2 mL)	600 (2 mL)	0
4–8 y	800/chewable	150/chewable	Ages 4–10 y: 700/1 softgel	200/chewable	10/chewable
>9 y	1600/2 softgels	300/2 chewables	Ages 10 and up: 1400/2 softgels	400/2 chewables	50/2 tablets
Zinc (mg)					
0–12 mo	5 (1 mL)	—	5 (1 mL)	7.5 (1 mL)	0
1–3 y	10 (2 mL)	—	10 (2 mL)	15 (2 mL)	0
4–8 y	15/chewable	7.5/chewable	Ages 4–10 y: 10/softgel	7.5/chewable	15/chewable
>9 y	30/2 softgels	15/2 chewables	Ages 10 and up: 20/2 softgels	15/2 chewables	22/2 tablets

Abbreviation: BC, beta carotene.

[a] The content of this Table was confirmed December 2008. Products also contain a full range of water-soluble vitamins; see SourceCF.com for content.

[b] CF-specific products.

[c] SourceCF Liquid, Chewables, and Softgels are registered trademarks of SourceCF Inc, a subsidiary of Eurand Pharmaceuticals, Inc.

[d] ADEK Chewables is a registered trademark of Axcan Pharma, Inc.

[e] AquADEKs Liquid and Softgels are registered trademarks of Yasoo Health Inc.

[f] Vitamax Drops and Chewables are registered trademarks of Shear/Kershman Labs, Inc.

[g] Poly-Vi-Sol Drops is a registered trademark of Mead Johnson and Company. Centrum Chewables and Tablets are registered trademarks of Wyeth Consumer Care.

[h] α-Tocopherol.

[i] Contains mixed tocopherols.

genetic mutations known to be associated with PI.[1] Clinical symptoms of PI include maldigestion with subsequent malabsorption, diarrhea, weight loss, poor growth, and nutrient deficiencies. Liver disease and small bowel disease can add to nutritional problems seen in CF. Patients with and without PI require careful nutrition management to avoid nutrition deficiencies. These deficiencies include fat- and water-soluble vitamins, minerals, essential fatty acids (EFAs), and trace elements. Deficiency states of a specific nutrient can occur due to decreased intake, maldigestion, increased losses, increased needs, oxidative stress, and possible metabolic abnormalities at the cellular level. For a comprehensive review of international nutrition recommendations, see the international foundation articles listed in **Box 1**.

ENERGY AND PROTEIN

Nutritional status, as measured by height and weight, is linked to survival.[2,3,4] There is an association between body mass index percentile and forced expiratory volume in 1 second (FEV_1).[5] Therefore, optimal energy intake is pivotal to the overall well-being of patients who have CF. Defining energy needs of patients with CF is a challenge. Individual variables include differences in maldigestion and resultant malabsorption,[6] pulmonary exacerbation,[7] pulmonary function,[8] fat-free mass,[9] gender,[6] pubertal status,[10] genetic mutation,[6,11] and age[12] and medical complications, including liver disease or CF-related diabetes. These variables make defining specific individual energy requirements challenging. Daily calorie recommendations provided by various CF societies range from 110% to 200%[5,13] of that recommended for individuals who do not have CF. To achieve the recommended energy goal, patients with CF often require a greater fat intake (35%–40% of energy).[14] A formula that incorporates level of activity, pulmonary function, and degree of malabsorption was included in the Cystic Fibrosis Foundation nutrition consensus report for use by clinicians in CF centers (**Table 2**). Formulas for calculating the energy needs of children with mild to moderate CF were evaluated, and the estimated energy requirement of the Dietary Reference Intake at the active level best estimated the energy needs of this particular group.[15,16] It is suggested that formulas be used as a starting point for calculating energy needs, but gain in weight and height, velocity of weight and height gain, and fat stores may provide a more objective measure of energy balance.[13,15] Energy intake is adjusted based on these objective measures.

Box 1
Foundation nutrition guidelines for children who have cystic fibrosis

Consensus report on nutrition for pediatric patients with cystic fibrosis, 2002.[14]

Nutrition in patients with cystic fibrosis: a European Consensus, 2002.[68]

Nutritional management of cystic fibrosis. UK Cystic Fibrosis Trust Nutrition Working Group, 2002.[156]

Consensus statement: guide to bone health and disease in cystic fibrosis, 2005.[51]

Australasian clinical practice guidelines for nutrition in cystic fibrosis, 2006.[13]

Antioxidants in cystic fibrosis. Conclusions from the CF Antioxidant Workshop, Bethesda, Maryland, November 11–12, 2003.[39]

Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review, 2008.[5]

Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis,submitted for publication[1]

Table 2
Determination of energy requirements according to the US Cystic Fibrosis Foundation

1. Calculate BMR in kcal from body weight in kg using World Health Organization equations[a]

Age range in years	Females	Males
0–3	61.0 wt − 51	60.9 wt − 54
3–10	22.5 wt + 499	22.7 wt + 495
10–18	12.2 wt + 746	17.5 wt + 651
18–30	14.7 wt + 496	15.3 wt + 679

2. Calculate the DEE by multiplying the BMR by activity plus disease coefficients

AC	Disease coefficients	DEE
Confined to bed: BMR × 1.3	FEV_1 > 80% predicted: 0	BMR × (AC + 0)
Sedentary: BMR × 1.5	FEV_1 40%–79% predicted: 0.2	BMR × (AC + 0.2)
Active: BMR × 1.7	FEV_1 < 40% predicted: 0.3 to 0.5[b]	BMR × (AC + 0.3)

3. Calculate total DERs from DEE and degree of steatorrhea

If a stool collection is not available to determine the fraction of fat intake, an approximate value of 0.85 may be used in the calculation. For PS patients and PI patients with a COA > 93% of intake, DER = DEE. For example: a patient with a COA of 0.78, the factor is 0.93/0.78 or 1.2. If the COA is not known the factor is 1.1.

Example: 10 year-old boy. Weight = 32 kg; AC = active; FEV_1% predicted = 85%; COA = not available.

12.2 (32) + 746 = 1136
1136 × (1.7 + 0) = 1931
1931 × 1.1 = 2124 calories per day

Abbreviations: AC, activity coefficients; BMR, basal metabolic rate; COA, coefficient of fat absorption; DEE, daily energy expenditure; DER, daily energy requirement.

[a] *From* World Health Organization. Energy and protein requirements [appendix B]. WHO Tech Rep Ser 1985;924(724):115–6.

[b] May range up to 0.5 with very severe lung disease.

Data from Ramsey BW, Farrell PM, Pencharz P. Nutritional assessment and management in cystic fibrosis: a consensus report. Am J Clin Nutr 1992;55:108–16.

Limited information is available describing specific dietary protein requirements for children who have CF. Studies assessing protein catabolism and protein deposition provide varying results, which may reflect differences in nutritional status and health of the subjects prior to the studies and caloric intake during the studies.[17,18] Protein intake is correlated with overall calorie intake, and in general, patients with CF who consume adequate calories also consume adequate protein.[13,19,20] Subgroups who do not meet energy or protein intake recommendations require nutrition intervention.[20,21] Studies providing oral or enteral supplements to increase overall energy and protein intake have provided conflicting results.[5,20,22]

FAT-SOLUBLE VITAMINS: A, E, D, AND K

The term, vitamin A, refers to a family of compounds important for cellular integrity, growth, immune function, and vision that is comprised of preformed retinoid and provitamin A carotenoids. Excessive retinol intake and elevated serum levels have raised concerns regarding potential toxicity to the liver and adverse impact on bone.[23,24] Vitamin A status is assessed by serum retinol status, by measuring serum retinol-binding protein, and by functional testing. Serum retinol is depressed during

acute inflammatory states but is not associated with disease severity.[25,26] There are no prospective randomized controlled trials demonstrating benefits of vitamin A supplementation on clinically relevant outcomes in CF.[27] To prevent deficiency states traditionally associated with CF, CF-specific multivitamins containing preformed, water-miscible retinol have been commercially available since 1993. Investigators have demonstrated elevated serum retinol in children, adolescents, and young adults with CF.[28] In response to concerns surrounding elevated serum retinol levels, several CF-specific multivitamins have lowered the retinol content and increased beta carotene (see **Table 1**).

Although serum retinol and retinol-binding protein are informative with respect to vitamin A adequacy, they are less informative regarding states of excess. Measurement of serum retinyl esters as a function of total serum retinol may be more informative for risk of toxicity and may be prudent to measure in this population.[29] Specific markers of hepatic injury and fibrosis also may need to be investigated in individuals with elevated serum vitamin A markers. Prospective studies of serum and tissue markers using newer, noninvasive techniques may be required to better determine vitamin A status across compartments and their relationships and to be able to better describe whole body status, from deficiency through adequacy to toxicity.[30] Regular surveillance to ensure adequacy and to avoid potential adverse effects may be indicated.

Vitamin E

Vitamin E includes eight chemically similar compounds, the most common being α-tocopherol; it is necessary for normal development, cell membrane stability, and prevention of hemolysis and important for its role as an antioxidant. Vitamin E requires bile, pancreatic juices, and dietary fat for optimal absorption, thereby putting patients with CF at risk for vitamin E deficiency if they do not receive adequate supplementation. Oxidative stress and a diet high in polyunsaturated fatty acids (PUFAs) may increase vitamin E needs in CF.[31] Reports of vitamin deficiency and its subsequent neurologic consequences in persons with CF have appeared in the literature[32,33] but are less common since the development of CF-specific multivitamins containing increased amounts of vitamin E. Low levels of vitamin E have been reported in PS patients.[34,35] Vitamin deficiency is present at the time of diagnosis in infants identified through newborn screening,[36] which, in some patients, continues into childhood.[37] Early, prolonged vitamin E deficiency can have a detrimental effect on cognitive function.[38] Therefore, the importance of initiating fat-soluble vitamin supplementation, especially vitamin E, at the time of diagnosis is paramount.[1] Vitamin E's role as an antioxidant in CF has been reviewed.[39] Varying results are reported describing the effect of vitamin E on lung function in patients with CF.[25,40,41] Serum/plasma vitamin E level is dependent on serum lipid levels and can be interpreted as a ratio to total cholesterol[42] or as a ratio to total lipids.[43] Extremes in lipid levels may influence interpretation of vitamin E results. To avoid detrimental effects of deficiency, vitamin E as contained in CF-specific multivitamins is started at diagnosis. Serum levels, best measured when patients are fasting, are assessed at least annually and vitamin E supplementation is adjusted as indicated.[14,44]

Vitamin D

Vitamin D is well known in association with bone health, but its role in maintaining health and preventing disease is still being explored.[45,46] Vitamin D deficiency is common in CF and found in infants diagnosed by newborn screening and in children and young adults.[37,47,48] Factors affecting vitamin D status in the general population and in CF include season, skin color, lack of exposure to sunlight, geographic location,

use of sunscreen, and inadequate dietary intake from supplements and foods, such as fatty fish and fortified foods.[45,46,49] In CF, additional factors include decreased absorption from PI and hepatobiliary dysfunction; increased catabolism due to medications, such as glucocorticoids; decreased capacity to convert the circulating serum 25-hydroxyvitamin D (25[OH]D) to the bioactive form, 1,25-(OH)2D; and decreased sunlight exposure during times of illness or treatment with some antibiotics.[50,51] Patients with reduced fat mass have decreased storage and may have decreased circulating vitamin D–binding protein.[51,52] Inadequate vitamin D intake led the American Academy of Pediatrics to increase the recommendation for vitamin D supplementation for infants and children.[53]

The total concentration of 25(OH)D (ie, 25[OH]D2 plus 25[OH]D3) reflects stores and is the accepted measure of vitamin D status.[49] Currently there is no universally accepted definition for vitamin D deficiency. For patients who have CF, it is defined as 25(OH)D level less than 30 ng/mL (75 nmol/L).[51] Treatment recommendations outlined in the Cystic Fibrosis Foundation Bone consensus report[51] may not correct low vitamin D levels.[54,55] Two forms of vitamin D are available in the United States, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D_3 is considered to have greater bioefficacy.[56,57] Suggested daily dose for toddlers and children who do not have CF or regular sun exposure is 1000 to 2000 international units of vitamin D_3.[45,46] In addition, treatment using sensible sun exposure and artificial UV-B light also has been explored.[45,49,58,59] Cod liver oil, with its risk for vitamin A toxicity, is not recommended.[46] The exact amount of vitamin D required to achieve normal blood levels for children with CF is not known. It may be prudent to start at doses recommended for persons who do not have CF, then repeat 25(OH)D levels in 2 to 3 months while they are still on therapy to monitor the adequacy of the treatment.[60]

Vitamin K

Maldigestion and resultant malabsorption from PI, bile salt deficiency, liver disease, bowel resection, or bacterial overgrowth; antibiotics; excessive vitamin E supplementation; and a diet inadequate in vitamin K–rich foods place children with CF at risk for vitamin K deficiency.[61,62,63] The best-known role of vitamin K is in coagulation; it also plays a role in bone metabolism.[61] Cerebral hemorrhage has been reported in CF infants prior to diagnosis and treatment.[64] Vitamin K deficiency may decrease bone formation and is associated with low bone mass; its aggressive supplementation improves markers of bone formation.[65,66] Assessing vitamin K status is a challenge. Circulating vitamin K_1 levels reflect recent dietary or supplement intake.[63] Prothrombin (or factor II) and osteocalcin (OC) are vitamin K–dependent proteins. Prothrombin is a delayed marker of hepatic vitamin K deficiency, as only 50% of its concentration is needed to maintain normal prothrombin time. Protein induced by vitamin K absence (PIVKA II) and undercarboxylated OC are more sensitive markers of vitamin K deficiency but not always clinically available.[61,67] Vitamin K supplementation recommendations range from 0.3 to 0.5 mg daily[14] to 1 mg daily to 10 mg weekly.[68] The optimal dose of vitamin K for children with CF is yet to be defined. Using markers of bone health to assess adequacy, suggested doses of vitamin K range from 1 mg daily to 10 mg weekly.[61,63,65,67,69,70] There are no known cases of vitamin K toxicity.[61]

WATER-SOLUBLE VITAMINS

Unlike for the fat-soluble vitamins, there are no specific water-soluble vitamin intake recommendations for patients with CF, perhaps due to the belief and some evidence that patients with CF who consume a balanced diet do not develop overt

deficiencies.[71] Additionally, in the United States, multivitamins designed for patients with CF contain a full complement of water-soluble vitamins that may prevent clinical evidence of deficiencies. There is limited work regarding the more subtle cellular activity of the water-soluble vitamins and CF. Acute illness; complications, such as liver or renal disease; and medication may compromise water-soluble vitamin nutrition. In 2001, McCabe reported three cases of riboflavin deficiency in children with CF who presented with angular stomatitis.[72] All of the children described were acutely ill and required supplemental riboflavin. In preliminary work, supplemental 5-methyltetrahydrofolate (the active form of folic acid) and vitamin B_{12} were given to a small group of persons who had CF.[73] Those subjects receiving the supplement demonstrated improved inflammatory response. Plasma ascorbic acid decreases with age, although the explanation for this is unclear.[74,75] Additional research is needed to define the water-soluble needs of patients with CF.

MINERALS: SODIUM CHLORIDE, CALCIUM, AND MAGNESIUM

The relationship of salty skin to characteristics typical of CF was noted as early as 1650.[76] Salt, as sodium and chloride, has played a key role in the diagnosis and management of CF. Patients with CF lose excessive salt through their skin: this is the basis for the pilocarpine-stimulated sweat test to diagnosis CF. There is some evidence that genotype may influence overall sodium and chloride losses in sweat, thereby possibly having an impact on dietary salt needs.[77,78,79] Currently, there is no conclusive evidence to adjust dietary sodium intake based on sweat test results. The body maintains a delicate system to maintain electrolyte balance, yet in CF, the endocrine and metabolic adaptations to salt depletion have not been well studied.[80] There are many reports of hypoelectrolytemia in the literature.[78,79,81] Human milk and baby formulas do not contain sufficient salt to meet the needs of infants who have CF. Electrolyte depletion in infants was noted when salt was removed from commercially available infant foods.[82] Older patients with CF also are at risk for electrolyte abnormalities,[83] resulting in lower serum osmolality during periods of excessive sweating, which may blunt the trigger to drink and cause what is referred to as ''voluntary dehydration.''[84] Electrolyte abnormalities should be considered in CF patients presenting with overt symptoms of salt depletion and with failure to thrive and anorexia. Patients admitted with metabolic acidosis with hypoelectrolytemia without renal disease may have undiagnosed CF. To avoid electrolyte abnormalities, patients with CF are recommended to consume a high salt diet. For infants, that includes the addition of salt to the diet. Two- to 4-mEq sodium/kg is generally recommended.[85] In CF care, 0.125 teaspoon of salt is recommended for newborns and for stable, growing infants, increased to 0.25 teaspoon at 6 months of age.[1] Care must be taken to assure that parents correctly dose salt to avoid complications of excessive sodium intake. Older patients are encouraged to eat a high-salt diet. For those persons active in warm environments, the addition of 0.25 teaspoon of salt to 12 oz of typical sports drinks may avoid voluntary dehydration.[86]

Calcium and magnesium are important in CF because of their role in bone health. Many variables have an impact on their adequacy, including vitamin D and K deficiency, inadequate dietary intake, and trapping in fat soaps due to malabsorption caused by PI, bile salt deficiency, and liver disease.[51] The calcium intake of children with CF needs to be monitored on a regular basis to optimize dietary intake for age[51,87,88] and to prevent hypocalcemia in patients placed on vitamin D supplementation. Monitoring of serum magnesium levels is important for patients with CF with renal insufficiency, low bone mineral density, or CF-related diabetes or when using

medications, such as aminoglycosides, that can cause renal tubular damage, and immunosuppressants, such as tacrolimus for transplant patients.[89,90,91,92]

TRACE ELEMENTS: ZINC, IRON, SELENIUM, AND COPPER

Zinc is a mineral involved in more than 300 functions in the body, including many related to pulmonary health, immunity, and growth.[93] Signs and symptoms of zinc deficiency are nonspecific and include lack of appetite, alterations in taste, growth failure, and disturbed immune function.[94,95] Zinc homeostasis is sensitive and maintained through the intestinal absorption of exogenous and endogenous zinc. Absorption is affected by the nutrient content of the diet and fat malabsorption,[96,97] placing persons who have CF at risk for zinc deficiency. Prior to initiation of PERT, infants with CF and PI are at risk for developing zinc deficiency due to malabsorption and increased endogenous losses.[98,99] Cases of acrodermatitis enteropathica-like rash due to zinc deficiency in infants and children prior to diagnosis with CF continue to be reported.[100,101] Lack of a clinically informative laboratory method and reference values to identify zinc deficiency makes diagnosing deficiency challenging. Reference values for zinc are dependent on the population and methods used to assess zinc levels.[102,103] Symptoms of zinc deficiency may occur while plasma levels are within normal reference ranges. The majority of zinc stores are intracellular and investigators suggest red blood cell zinc as a better indicator of zinc status.[104] In zinc supplementation trials, patients with CF and decreased serum zinc concentrations seem to benefit the most from supplementation.[102,105,106] Empiric zinc supplementation for 6 months has been recommended for children with CF exhibiting growth failure, vitamin A deficiency, or night blindness refractory to vitamin A therapy.[14,44]

Anemia is frequently seen in patients with CF and is associated with poorer lung function and vitamin deficiency.[107] The incidence of iron deficiency anemia ranges from 33% in children to 74% in older patients with CF.[108,109,110] Anemia can be due to true iron deficiency or anemia of chronic disease.[111] The etiology of iron deficiency may be related to decreased dietary intake, increased losses in sputum and the gastrointestinal tract, and possibly the severity of suppurative lung disease.[112,113] Evidence indicates that iron deficiency is not related to PERT.[112] It has been shown that *Pseudomonas aeruginosa* actively acquires iron from the proteins in the host airway, secretes siderophores (iron-chelating compounds) to acquire iron, and produces inflammatory cytokines, which results in anemia of chronic disease.[112,113] Iron deficiency is difficult to diagnose in patients with CF and has to be differentiated from anemia of chronic disease. Obtaining soluble transferrin receptor levels is recommended in addition to checking iron, transferrin, and ferritin levels.[109] There is some controversy regarding supplementation because some investigators believe that providing iron allows pseudomonas bacteria to grow. It is generally accepted, however, that if a true iron deficiency exists, it should be treated, whereas in anemia of chronic disease, the underlying inflammation needs to be treated and iron supplements withheld.

Selenium is a known antioxidant. Low selenium levels have been seen in patients with CF,[39,114,115] and supplementation with selenium containing PERT resulted in increased plasma selenium levels and gluthathione peroxidase activity.[114] Possible reasons for low levels include abnormalities in dietary intake, absorption, and metabolism and increased needs due to increased oxidative stress. Supplementation trials of selenium alone have not been shown to be effective,[116] although a trial in which selenium was one of many antioxidants given showed improved plasma levels and an increase in predicted FEV_1.[31]

Not much is known about copper metabolism in patients with CF. Persistent anemia unresponsive to iron supplements may be related to copper deficiency. Variable results have been found for serum copper and ceruloplasmin levels in patients with CF. Because inflammation can raise copper and ceruloplasmin levels, checking these levels in the presence of inflammation renders them less reliable. Reduced levels of copper enzyme activity (cytochrome oxidase and copper-zinc superoxide dismutase) have been seen in monocytes and neutrophils in patients with CF, suggesting a functional deficiency.[117,118,119]

POLYUNSATURATED AND ESSENTIAL FATTY ACIDS, CHOLINE, GLUTATHIONE, AND COENZYME Q10

Individuals who have CF are prone to PUFA abnormalities. Linoleic acid (LA) (ω-6) and α- linolenic acid (ω-3) are the EFAs; humans cannot synthesize them and are reliant on dietary sources to ensure adequacy and prevent deficiency. EFA and long-chain PUFAs have a variety of structural and functional roles throughout the life cycle, including cell signaling, gene expression via peroxisome proliferator-activated receptors, and proinflammatory activity via the eicosanoid pathways. EFA deficiency (EFAD) was first described in CF in 1962.[120] EFAD was present at the time of diagnosis, with classic clinical manifestations of alopecia, easy bruisability, desquamating skin rashes, and suboptimal growth. Although these symptoms may still occur, biochemical evidence of EFAD can be present in otherwise apparently well-nourished individuals.[121] The etiology is most likely multifactorial and may include fat malabsorption[122] and abnormal membrane release and metabolism.[123,124] EFAD has been found in association with ceramide deficiency,[125] CF genotype, and pancreatic status.[126,127] EFAD is typically associated with a blunted inflammatory response in otherwise healthy individuals; however, patients with CF, paradoxically, develop a more pronounced inflammatory effect.[128]

The two most frequently described PUFA abnormalities in CF are LA (the ω-6 EFA) deficiency and decrease in docosahexaenoic acid (DHA).[129,130] Serum LA status has been associated with clinically important outcomes of growth and pulmonary status.[131,132] Similar associations have not been observed with the triene:tetraene ratio,[133] suggesting serum LA status may be a more relevant indicator of EFA status in patients with CF. LA supplementation studies have demonstrated that improvement of LA status or ''normalization'' or ''approching level of those in healthy individuals'' is possible.[134] DHA is important in retinal and brain development and down-regulates the eicosanoid-mediated inflammatory response compared to arachidonic acid, which has a proinflammatory influence. Several short-term DHA supplementation trials have been performed to date. The supplements have been well tolerated without adverse health effects and were associated with an improvement of serum and tissue DHA status and a decrease of arachidonic acid:DHA ratio.[135,136,137] Furthermore, investigators have demonstrated that patients with CF supplemented with DHA have improved leukotriene B4 and other anti-inflammatory eicosanoids and cytokines.[138,139] Associations between DHA status, supplementation, and clinically significant outcomes (eg, pulmonary function and growth), however, have not been reported. Prevention of deficiency and attainment of adequacy is the first goal in the nutritional management of EFA deficiency and PUFA abnormalities in patients with CF. Alternatively, the goal could be attainment of serum PUFA profiles associated with optimal clinical outcomes, as proposed by Christophe and Robberecht,[140] but more research is required.

Choline

Choline is an essential nutrient and has myriad structural and functional roles, including cell membrane function, as a methyl donor intersecting with the folate, homocysteine-methionine, and DNA repair pathways. Choline is an essential nutrient with a dietary requirement.[141] Subjects with CF are prone to choline deficiency and to altered membrane phospholipid status.[142] This may be related to increase membrane turnover[142] and to dietary phospholipid malabsorption.[143] Supplementation with choline or its metabolites has been associated with improved serum choline status and profiles approaching that of healthy control subjects.[144]

Glutathione

Glutathione (GSH) is involved in several cellular processes, including cell differentiation, proliferation, apoptosis, redox reactions as an antioxidant, phospholipid metabolism, and immune system function. As such, GSH is often expressed as a ratio reflecting its redox state to GSH disulphide (GSSG). Alterations of GSH:GSSG occur during inflammation.[145] GSH concentrations in lung epithelial lining fluid (ELF) are decreased in patients with CF compared to healthy subjects and in other tissue compartments.[146,147] This may have an impact on viscosity and the inflammatory response in these different tissues compartments, particularly in the ELF. Low GSH concentrations maybe related to CF transmembrane regulator abnormalities and increased consumption due to increased oxidative stress and inflammation. Additionally, as seen in the CF mouse model, exposure to *Pseudomonas aeruginosa* is met with decreased export of GSH to the ELF, which in part may explain the difficulty in clearing such infections in patients with CF.[148] Choline supplementation trials in CF have shown improvements of GSH and the ratio of GSH to GSSG.[144] Oral intake of *N*-acetylcysteine has shown increased blood neutrophil GSH concentrations and decreased sputum elastase activity.[149] Aerosolized delivery of GSH and related compounds can result in bronchospasm.[150] Aerosolized GSH, however, has been associated with decreased prostaglandin E2 (proinflammatory) concentrations in bronchial fluids and improved post-treatment lung function in patients with CF.[151] *S*-nitrosoglutathione, another GSH entity normally found in pulmonary tissue, causes airway smooth muscle relaxation and improved ciliary function and is decreased in subjects with CF.[152] Clinical trials of aerosolized *S*-nitrosoglutathione have been performed in CF[153] but are not indicated for routine clinical use at this time.[39]

Coenzyme Q10

Also referred to as ubiquinone, coenzyme Q10 (COQ10) is a lipid-soluble, mitochondrial membrane–based constituent of the electron transport chain, which aids in maintaining vitamin E in a reduced state, thus contributing to the body's antioxidant system. The majority of COQ10 is synthesized along cholesterol synthesis pathways, with approximately 25% obtained from dietary sources of animal protein. Total plasma concentrations of COQ10 were found decreased in subjects with CF as compared to healthy controls.[154] Deficiency in subjects with CF seems to be related more to inadequate intake and malabsorptive losses than to oxidative stress or increased turnover.[155] A subsequent longitudinal study in subjects with CF reported decreased total serum COQ10 concentrations more frequently in subjects with CF and PI compared to those with CF and PS. Low levels of COQ10 are associated with total lipids, beta carotene, and α-tocopherol.[154] Prospective supplementation studies are required to further define effects on tissue compartment status, oxidative stress status, and clinical outcomes.

SUMMARY

Nutrition continues to be a challenge in the care of patients with CF. In the past, the goal was to provide adequate calories to insure survival; now, the goals are to optimize nutrient intake to promote normal growth and nutritional status, avoid overt and subtle nutrient deficiencies, and modulate inflammation. Compared to the general population, there is little evidence to support precise nutrition recommendations for patients with CF, although efforts have been made to use available evidence to set care standards (see **Box 1**). More research is required to address these concerns and gaps in current knowledge.

REFERENCES

1. Borowitz D, Robinson KA, Rosenfeld M, et al. CFF practice guidelines for the management of infants with cystic fibrosis during the first two years of life. J Pediatr, in press.
2. Corey M, McLaughlin FJ, Williams M, et al. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. J Clin Epidemiol 1988;41(6):583–91.
3. Beker LT, Russek-Cohen E, Fink RJ. Stature as a prognostic factor in cystic fibrosis survival. J Am Diet Assoc 2001;101(4):438–42.
4. Sharma R, Florea VG, Bolger AP, et al. Wasting as an independent predictor of mortality in patients with cystic fibrosis. Thorax 2001;56:746–50.
5. Stallings VA, Stark LJ, Robinson KA, et al. 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 systematic review. J Am Diet Assoc 2008;108(5):832–9.
6. Allen JR, McCauley JC, Selby AM, et al. Differences in resting energy expenditure between male and female children with cystic fibrosis. J Pediatr 2003;142: 15–9.
7. Reilly JJ, Ralston JM, Paton JY, et al. Energy balance during acute respiratory exacerbation in children with cystic fibrosis. Eur Respir J 1999;13:804–9.
8. Fried MD, Durie PR, Tsui LC, et al. The cystic fibrosis gene and resting energy expenditure. J Pediatr 1991;119(6):913–6.
9. Stallings VA, Tomezsko JL, Schall JI, et al. Adolescent development and energy expenditure in females with cystic fibrosis. Clin Nutr 2005;24:737–45.
10. Barclay A, Allen JR, Blyler E, et al. Resting energy expenditure in females with cystic fibrosis: is it affected by puberty? Eur J Clin Nutr 2007;61:1207–12.
11. Magoffin A, Allen JR, McCauley J, et al. Longitudinal analysis of resting energy expenditure in patients with cystic fibrosis. J Pediatr 2008;152:703–8.
12. Bines JE, Truby HD, Armstrong DS, et al. Energy metabolism in infants with cystic fibrosis. J Pediatr 2002;140:527–33.
13. Australasian clinical practice guidelines for nutrition in cystic fibrosis. 2005. Available at: http://.cysticfibrosis.org.au/pdf/CF_Nutrition_Guidelines.pdf. Accessed July 28, 2009.
14. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2002;35(3):246–59.
15. Trabulsi J, Ittenbach RF, Schall JI, et al. Evaluation of formulas for calculating total energy requirements of preadolescent children with cystic fibrosis. Am J Clin Nutr 2007;85:144–51.

16. Institute of Medicine. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. Washington, DC: National Academy Press; 2002.
17. Vaisman N, Clarke R, Rossi M, et al. Protein turnover and resting energy expenditure in patients with undernutrition and chronic lung disease. Am J Clin Nutr 1992;55:63–9.
18. Geukers VGM, Oudshoorn JH, Taminiau JAJM, et al. Short-term protein intake and stimulation of protein synthesis in stunted children with cystic fibrosis. Am J Clin Nutr 2005;81:605–10.
19. Kawchak DA, Zhoa H, Scanlin TF, et al. Longitudinal, prospective analysis of dietary intake in children with cystic fibrosis. J Pediatr 1996;129:119–29.
20. White H, Morton AM, Peckham DG, et al. Dietary intakes in adult patients with cystic fibrosis-do they achieve guidelines? J Cyst Fibros 2003;3:1–7.
21. Schall JI, Bentley T, Stallings VA. Meal patterns, dietary fat intake and pancreatic enzyme use in preadolescent children with cystic fibrosis. J Pediatr Gastroenterol Nutr 2006;43:651–9.
22. Poustie VJ, Russell JE, Watling RM, et al. Oral protein energy supplements for children with cystic fibrosis: CALICO multicentre randomized controlled trial. BMJ 2006;332:632–6.
23. Institute of Medicine. Dietary reference intakes for vitamin A, vitamin K, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, vanadium, and zinc. Washington, DC: National Academy Press; 2001.
24. Michaelsson K, Lithell H, Vessby B, et al. Serum retinol levels and the risk of fracture. N Engl J Med 2003;348:287–94.
25. Hakim F, Kerem E, Rivlin J, et al. Vitamins A and E and pulmonary exacerbations in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2007;45(3):347–53.
26. Duggan C, Colin AA, Agil A, et al. Vitamin A status in acute exacerbations of cystic fibrosis. Am J Clin Nutr 1996;64(4):635–9.
27. O'Neil C, Shevill E, Chang AB. Vitamin A supplementation for cystic fibrosis. Cochrane Database Syst Rev 2008;23(1):CD006751.
28. Maqbool A, Graham-Maar RC, Schall JI, et al. Vitamin A intake and elevated serum retinol levels in children and young adults with cystic fibrosis. J Cyst Fibros 2008;7(2):137–41 [Epub 2007 Sep 4].
29. James DR, Owen G, Campbell IA, et al. Vitamin A absorption in cystic fibrosis: risk of hypervitaminosis A. Gut 1992;33(5):707–10.
30. Tanumihardjo SA. Assessing vitamin A status: past, present and future. J Nutr 2004;134(1):290S–3S.
31. Wood LG, Fitzgerald DA, Lee AK, et al. Improved antioxidant and fatty acid status of patients with cystic fibrosis after antioxidant supplementation is linked to improved lung function. Am J Clin Nutr 2003;77:150–9.
32. Willison HJ, Muller DPR, Matthews S, et al. A study of the relationship between neurological function and serum vitamin E concentrations in patients with cystic fibrosis. J Neurol Neurosurg Psychiatry 1985;48:1097–102.
33. Cynamon HA, Milov DE, Valenstein E, et al. Effect of vitamin E deficiency on neurologic function in patients with cystic fibrosis. J Pediatr 1988;113:637–40.
34. Lancellotti L, D'Orazio C, Mastella G, et al. Deficiency of vitamins E and A in cystic fibrosis is independent of pancreatic function and current enzyme and vitamin supplementation. Eur J Pediatr 1996;155:281–5.
35. Dorlochter L, Aksnes L, Fluge G. Faecal elastase-1 and fat-soluble vitamin profiles in patients with cystic fibrosis in Western Norway. Eur J Nutr 2002;41: 148–52.

36. Sokol RJ, Reardon MC, Accurso FJ, et al. Fat-soluble-vitamin status during the first year of life in infants with cystic fibrosis identified by screening of newborns. Am J Clin Nutr 1989;50:1064–71.
37. Feranchak AP, Sontag MK, Wagener JS, et al. Prospective, long-term study of fat-soluble vitamin status in children with cystic fibrosis identified by newborn screen. J Pediatr 1999;135:601–10.
38. Koscik RL, Lai HC, Laxova A, et al. Preventing early, prolonged vitamin E deficiency: an opportunity for better cognitive outcomes via early diagnosis through neonatal screening. J Pediatr 2005;147:S51–6.
39. Cantin AM, White TB, Cross CE, et al. Antioxidants in cystic fibrosis. Conclusions from the CF antioxidant workshop, Bethesda, Maryland, November 11–12, 2003. Free Radic Biol Med 2007;42:15–31.
40. Bines JE, Truby HD, Armstrong DS, et al. Vitamin A and E deficiency and lung disease in infants with cystic fibrosis. J Paediatr Child Health 2005;41:663–8.
41. Oudshoorn JH, Klijn PH, Hofman Z, et al. Dietary supplementation with multiple micronutrients: no beneficial effects in pediatric cystic fibrosis patients. J Cyst Fibros 2007;6:35–40.
42. Huang SH, Schall JI, Zemel BS, et al. Vitamin E status in children with cystic fibrosis and pancreatic insufficiency. J Pediatr 2006;148:556–9.
43. Sokol RJ. Selection bias and vitamin E status in cystic fibrosis. J Pediatr 2007; 150(5):e85.
44. Tinley CG, Withers NJ, Sheldon CD, et al. Zinc therapy for night blindness in cystic fibrosis. J Cyst Fibros 2008;7:333–5.
45. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
46. Cannell JJ, Hollis BW, Zasloff M, et al. Diagnosis and treatment of vitamin D deficiency. Expert Opin Pharmacother 2008;9(1):107–18.
47. Neville LA, Ranganathan SC. Vitamin D in infants with cystic fibrosis diagnosed by newborn screening. J Paediatr Child Health 2009;45(1–2):36–41.
48. Rovner AJ, Stallings VA, Schall JI, et al. Vitamin D insufficiency in children, adolescents, and young adults with cystic fibrosis despite routine oral supplementation. Am J Clin Nutr 2007;86:1694–9.
49. Brannon PM, Yetley EA, Bailey RL, et al. Overview of the conference "Vitamin D and health in the 21st Century: an update". Am J Clin Nutr 2008;88(Suppl): 483S–90S.
50. Lark RK, Lester GE, Ontjes DA, et al. Diminished and erratic absorption of ergocalciferol in adult cystic fibrosis patients. Am J Clin Nutr 2001;73:602–6.
51. Aris RM, Merkel PA, Bachrach LK, et al. Consensus statement: guide to bone health and disease in cystic fibrosis. J Clin Endocrinol Metab 2005;90:1888–96.
52. Speeckaert MM, Wehlou C, Vandewalle S, et al. Vitamin D binding protein, a new nutritional marker in cystic fibrosis patients. Clin Chem Lab Med 2008;46(3): 365–70.
53. Wagner LW, Greer FR, The Section on Breastfeeding and Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics 2008;122:1142–52.
54. Green D, Carson K, Leonard A, et al. Current treatment recommendations for correcting vitamin D deficiency in pediatric patients with cystic fibrosis are inadequate. J Pediatr 2008;153:554–9.
55. Virella-Lowell I, Bowman C, Wagner C, et al. Successful supplementation of vitamin D in cystic fibrosis. Pediatr Pulmonol 2006;29(Suppl):396.
56. Armas LAG, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab 2004;89:5387–91.

57. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D2) as a vitamin supplement. Am J Clin Nutr 2006;84:694–7.
58. Gronowitz E, Larko O, Gilljam M, et al. Ultraviolet B radiation improves serum levels of vitamin D in patients with cystic fibrosis. Acta Paediatr 2005;94:547–52.
59. Khazai NB, Judd S, Jeng L, et al. Treatment and prevention of vitamin D insufficiency in cystic fibrosis patients: comparative efficacy of ergocalciferol, cholecalciferol and UV light. J Clin Endocrinol Metab 2009;94:2037–43.
60. Aris R. Update on bone mineralization in CF. Pediatr Pulmonol 2008;31(Suppl): 173–5.
61. Conway SP. Vitamin K in cystic fibrosis. J R Soc Med 2004;97(Suppl 44):48–51.
62. Booth SL, Golly I, Sacheck J, et al. Effect of vitamin E supplementation on vitamin K status in adults with normal coagulation status. Am J Clin Nutr 2004; 80(1):143–8.
63. Drury D, Grey VL, Ferland G, et al. Efficacy of high dose phylloquinone in correcting vitamin K deficiency in cystic fibrosis. J Cyst Fibros 2008;7:457–9.
64. Hamid B, Khan A. Cerebral hemorrhage as the initial manifestation of cystic fibrosis. J Child Neurol 2007;22(1):114–5.
65. Nicolaidou P, Stavrinadis I, Loukou I, et al. The effect of vitamin K supplementation on biochemical markers of bone formation in children and adolescents with cystic fibrosis. Eur J Pediatr 2006;165:540–5.
66. Fewtrell MS, Benden C, Williams JE, et al. Undercarboxylated osteocalcin and bone mass in 8–12 year old children with cystic fibrosis. J Cyst Fibros 2008; 7(4):307–12.
67. Mosler K, von Kries R, Vermeer C, et al. Assessment of vitamin K deficiency in CF—how much sophistication is useful? J Cyst Fibros 2003;2:91–6.
68. Sinaasappel M, Stern M, Littlewood J, et al. Nutrition in patients with cystic fibrosis: a European Consensus. J Cyst Fibros 2002;1:51–75.
69. Urquhart DS, Fitzpatrick M, Cope J, et al. Vitamin K prescribing patterns and bone health surveillance in UK children with cystic fibrosis. J Hum Nutr Diet 2007;20:605–10.
70. van Hoorn JHL, Hendriks JJE, Vermeer C, et al. Vitamin K supplementation in cystic fibrosis. Arch Dis Child 2003;88:974–5.
71. Solomons NW, Wagonfeld JB, Rieger C, et al. Some biochemical indices of nutrition in treated cystic fibrosis patients. Am J Clin Nutr 1981;34:462–74.
72. McCabe H. Riboflavin deficiency in cystic fibrosis: three case reports. J Hum Nutr Diet 2001;14:365–70.
73. Scambi C, DeFranceschi L, Guarini P, et al. Preliminary evidence for cell membrane amelioration n children with cystic fibrosis by 5-MTHF and vitamin B12 supplementation: a single arm trial. PLoS One 2009;4(3):e4782.
74. Winklhofer-Roob BM, Ellemunter H, Fruhwirth M, et al. Plasma vitamin C concentrations in patients with cystic fibrosis: evidence of associations with lung inflammation. Am J Clin Nutr 1997;65:1858–66.
75. Back EI, Frindt C, Nohr D, et al. Antioxidant deficiency in cystic fibrosis: when is the right time to take action? Am J Clin Nutr 2004;80:374–84.
76. Taussig LM. Cystic fibrosis. New York: Thieme-Stratton, Inc; 1984.
77. Leoni GB. A specific cystic fibrosis mutation (T3381) associated with the phenotype of isolated hypotonic dehydration. J Pediatr 1995;127:281–3.
78. Fustik S, Pop-Jordanova N, Slaveska N, et al. Metabolic alkalosis with hypoelectrolytemia in infants with cystic fibrosis. Pediatr Int 2002;44:289–92.
79. Yalcin E. Clinical features and treatment approaches in cystic fibrosis with pseudo-Bartter syndrome. Ann Trop Paediatr 2005;25:119–24.

80. Legris GJ, Dearborn D, Stern RC. Sodium space and intravascular volume: dietary sodium effects in cystic fibrosis and healthy subjects. Pediatrics 1998;101: 48–56.
81. Kessler WR, Anderson DH. Heat prostration in fibrocystic disease of the pancreas and other conditions. Pediatrics 1951;8:648–56.
82. Laughlin JJ, Brady MS, Eigen H. Changing feeding trends as a cause of electrolyte depletion in infants with cystic fibrosis. Pediatrics 1981;68:203–7.
83. Orenstein DM, Henke KG, Costill DL, et al. Exercise and heat stress in cystic fibrosis patients. Pediatr Res 1983;17:267–9.
84. Bar-Or O, Blimkie CJR. Voluntary dehydration and heat intolerance in cystic fibrosis. Lancet 1992;339:696–9.
85. Chan DS. Recommended daily allowance of maintenance parenteral nutrition in infants and children. Am J Health Syst Pharm 1995;52:651–3.
86. Kriemler S, Wilk B, Schurer W, et al. Preventing dehydration in children with cystic fibrosis who exercise in the heat. Med Sci Sports Exerc 1993;31:774–9.
87. Heaney RP, Weaver CM. Newer perspectives on calcium nutrition and bone quality. J Am Coll Nutr 2005;24(Suppl 6):574S–81S.
88. Schulze KJ, Cutchins C, Rosenstein BJ, et al. Calcium acquisition rates do not support age-appropriate gains in total body bone mineral content in prepuberty and late puberty in girls with cystic fibrosis. Osteoporos Int 2006;17(5):731–40.
89. von Vigier RO, Truttmann AC, Zindler-Schmocker K, et al. Aminoglycosides and renal magnesium homeostasis in humans. Nephrol Dial Transplant 2000;15: 822–6.
90. Greer RM, Buntain HM, Potter JM, et al. Abnormalities of the PTH-vitamin D axis and bone turnover markers in children, adolescents and adults with cystic fibrosis: comparison to healthy controls. Osteoporos Int 2003;14:404–11.
91. Glass S, Plant ND, Spencer DA. The effects of intravenous tobramycin on renal tubular function in children with cystic fibrosis. J Cyst Fibros 2005;4:221–5.
92. Gupta A, Eastham KM, Wrightson N, et al. Hypomagnesemia in cystic fibrosis patients referred for lung transplant assessment. J Cyst Fibros 2007;6:360–2.
93. Prasad AS. Zinc deficiency in women, infants, and children. J Am Coll Nutr 1996; 15:113–20.
94. Mocchegiani E, Provinciali M, Di Stefano G, et al. Role of the low zinc bioavailability on cellular immune effectiveness in cystic fibrosis. Clin Immunol Immunopathol 1995;75:214–24.
95. Cantin AM. Potential for antioxidant therapy of cystic fibrosis. Curr Opin Pulm Med 2004;10:531–6.
96. Krebs NF. Overview of zinc absorption and excretion in the human gastrointestinal tract. J Nutr 2000;130(Suppl 5S):1374S–7S.
97. Easley D, Krebs N, Jefferson M, et al. Effect of pancreatic enzymes on zinc absorption in cystic fibrosis. J Pediatr Gastroenterol Nutr 1998;26:136–9.
98. Krebs NF, Sontag M, Accurso FJ, et al. Low plasma zinc concentrations in young infants with cystic fibrosis. J Pediatr 1998;133:761–4.
99. Krebs NF, Westcott JE, Arnold TD, et al. Abnormalities in zinc homeostasis in young infant with cystic fibrosis. Pediatr Res 2000;48:256–61.
100. Crone J, Huber WD, Eichler I, et al. Acrodermatitis enteropathica-like eruption as the presenting sign of cystic fibrosis-case report and review of the literature. Eur J Pediatr 2002;161:475–8.
101. Bernstein ML, McCusker MM, Grant-Kels JM. Cutaneous manifestations of cystic fibrosis. Pediatr Dermatol 2008;25:150–7.

102. Abdulhamid I, Beck FW, Millard S, et al. Effect of zinc supplementation on respiratory tract infections in children with cystic fibrosis. Pediatr Pulmonol 2008;43: 281–7.
103. Maqbool A, Schall JI, Zemel BS, et al. Plasma zinc and growth status in preadolescent children with cystic fibrosis. J Pediatr Gastroenterol Nutr 2006;43: 95–101.
104. Akanli L, Lowenthal DB, Gjonaj S, et al. Plasma and red blood cell zinc in cystic fibrosis. Pediatr Pulmonol 2003;35:2–7.
105. Van Biervliet S, Van Biervliet JP, Robberecht E. Serum zinc in patients with cystic fibrosis at diagnosis and after one year of therapy. Biol Trace Elem Res 2006; 112:205–11.
106. Van Biervliet S, VandeVelde S, Van Biervliet JP, et al. The effect of zinc supplements in cystic fibrosis patients. Ann Nutr Metab 2008;52:152–6.
107. von Drygalski A, Biller J. Anemia in CF: incidence, mechanisms, and association with pulmonary function and vitamin deficiency. Nutr Clin Pract 2008;23(5): 557–63.
108. Keevil B, Rowlands D, Burton I, et al. Assessment of iron status in CF patients. Ann Clin Biochem 2000;37(Pt 5):662–5.
109. Khalid S, McGrowder D, Kemp M, et al. The use of soluble transferring receptor to assess iron deficiency in adults with cystic fibrosis. Clin Chim Acta 2007; 378(1–2):194–200.
110. Fischer R, Simmerlein R, Huber RM, et al. Lung disease severity, chronic inflammation, iron deficiency and erythropoietin response in adults with CF. Pediatr Pulmonol 2007;42(12):1193–7.
111. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352: 1011–23.
112. Reid DW, Withers NJ, Francis L, et al. Iron deficiency in CF. Relationship to lung disease severity and chronic pseudomonas aeruginosa infection. Chest 2002; 121(1):48–54.
113. Reid DW, Lam QT, Schneider H, et al. Airway iron and iron-regulatory cytokines in CF. Eur Respir J 2004;24(2):286–91.
114. Winklhofer-Roob BM, Tiran B, Tuchschmid PE, et al. Effects of pancreatic enzyme preparations on erythrocyte glutathione peroxidase activities and plasma selenium concentrations in CF. Free Radic Biol Med 1998;25(2): 242–9.
115. Michaike B. Selenium speciation in human serum of CF patients compared to serum from healthy persons. J Chromatogr A 2004;1058(1–2):203–8.
116. Portal B, Richard MJ, Coudray C, et al. Effect of double-blind cross-over selenium supplementation on lipid peroxidation markers in CF patients. Clin Chim Acta 1995;234(1–2):137–46.
117. Percival SS, Bowser E, Wagner M. Reduced copper enzyme activities in blood cells of children with CF. Am J Clin Nutr 1995;62:633–8.
118. Percival SS, Kauwell GPA, Bowser E, et al. Altered copper status I adult men with CF. J Am Coll Nutr 1999;18(6):614–9.
119. Best K, McCoy K, Gemma S, et al. Copper enzyme activities in CF before and after copper supplementation plus or minus zinc. Metabolism 2004;53(1):37–41.
120. Kuo PT, Huang NN, Bassett R. The fatty acid composition of the serum chylomicrons and adipose tissue of children with cystic fibrosis of the pancreas. J Pediatr 1962;60:394–403.
121. Roulet M, Frascarolo P, Rappaz I, et al. Essential fatty acid deficiency in well nourished young cystic fibrosis patients. Eur J Pediatr 1997;156:952–6.

122. Kalivianakis M, Minich DM, Bijleveld CM, et al. Fat malabsorption in cystic fibrosis patients receiving enzyme replacement therapy is due to impaired intestinal uptake of long-chain fatty acids. Am J Clin Nutr 1999;69(1):127–34.
123. Carlstedt-Duke J, Bronnegard M, Strandvik B. Pathological regulation of arachidonic acid release in cystic fibrosis: the putative basic defect. Proc Natl Acad Sci U S A 1986;83:9202–6.
124. Freedman SD, Katz MH, Parker EM, et al. A membrane lipid imbalance plays a role in the phenotypic expression of cystic fibrosis in cftr(-/-) mice. Proc Natl Acad Sci U S A 1999;96(24):13995–4000.
125. Guilbault C, Wojewodka G, Saeed Z, et al. Cystic fibrosis fatty acid imbalance is linked to ceramide deficiency and corrected by fenretinide. Am J Respir Cell Mol Biol 2009;41:100–6 2008 Dec 4 [Epub ahead of print].
126. Strandvik B, Gronowitz E, Enlund F, et al. Essential fatty acid deficiency in relation to genotype in patients with cystic fibrosis. J Pediatr 2001;139(5):650–5.
127. Freedman SD, Blanco PG, Zaman MM, et al. Association of cystic fibrosis with abnormalities in fatty acid metabolism. N Engl J Med 2004;350(6):560–9.
128. Strandvik B, Svensson E, Seyberth HW. Prostanoid biosynthesis in patients with cystic fibrosis. Prostaglandins Leukot Essent Fatty Acids 1996;55(6): 419–25.
129. Coste T, Armand M, Lebacq J, et al. An overview of monitoring and supplementation of omega 3 fatty acids in cystic fibrosis. Clin Biochem 2007;40:511–20.
130. Cawood AL, Carroll MP, Wootton SA, et al. Is there a case for n-3 fatty acid supplementation in cystic fibrosis? Curr Opin Clin Nutr Metab Care 2005;8: 153–9.
131. Shoff SM, Ahn HY, Davis L, et al. Temporal associations among energy intake, plasma linoleic acid, and growth improvement in response to treatment initiation after diagnosis of cystic fibrosis. Pediatrics 2006;117:391–400.
132. Walkowiak J, Lisowska A, Blaszczynski M, et al. Polyunsaturated fatty acids in cystic fibrosis are related to nutrition and clinical expression of the disease. J Pediatr Gastroenterol Nutr 2007;45:488–90.
133. Maqbool A, Schall JI, Garcia-Espana JF, et al. 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):635–44.
134. Lloyd-Still JD, Johnson SB, Holman RT. Essential fatty acid status in cystic fibrosis and the effects of safflower oil supplementation. Am J Clin Nutr 1981; 34(1):1–7.
135. Lloyd-Still JD, Powers CA, Hoffman DR, et al. Bioavailability and safety of a high dose of docosahexaenoic acid triacylglycerol of algal origin in cystic fibrosis patients: a randomized, controlled study. Nutrition 2006;22:36–46.
136. Van Biervliet S, Devos M, Delhaye T, et al. Oral DHA supplementation in DeltaF508 homozygous cystic fibrosis patients. Prostaglandins Leukot Essent Fatty Acids 2008;78(2):109–15 [Epub 2008 Feb 13].
137. McKarney C, Everard M, N'Diaye T. Omega-3 fatty acids (from fish oils) for cystic fibrosis. Cochrane Database Syst Rev 2007;17(4):CD002201.
138. Kurlandsky LE, Bennink MR, Webb PM, et al. The absorption and effect of dietary supplementation with omega-3 fatty acids on serum leukotriene B4 in patients with cystic fibrosis. Pediatr Pulmonol 1994;18:211–7.
139. Panchaud A, Sauty A, Kernen Y, et al. Biological effects of a dietary omega-3 polyunsaturated fatty acids supplementation in cystic fibrosis patients: a randomized, crossover placebo-controlled trial. Clin Nutr 2006;25(3): 418–27.

140. Christophe A, Robberecht E. Directed modification instead of normalization of fatty acid patterns in cystic fibrosis: an emerging concept. Curr Opin Clin Nutr Metab Care 2001;4(2):111–3.
141. Institute of Medicine. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998.
142. Ulane MM, Butler JD, Peri A, et al. Cystic fibrosis and phosphatidylcholine biosynthesis. Clin Chim Acta 1994;230(2):109–16.
143. Chen AH, Innis SM, Davidson AG, et al. Phosphatidylcholine and lysophosphatidylcholine excretion is increased in children with cystic fibrosis and is associated with plasma homocysteine, S-adenosylhomocysteine, and S-adenosylmethionine. Am J Clin Nutr 2005;81(3):686–91.
144. Innis SM, Davidson AG, Melynk S, et al. Choline-related supplements improve abnormal plasma methionine-homocysteine metabolites and glutathione status in children with cystic fibrosis. Am J Clin Nutr 2007;85(3):702–8.
145. Ballatori N, Krance SM, Notenboom S, et al. Glutathione dysregulation and the etiology and progression of human diseases. Biol Chem 2009;390(3):191–214 [Epub ahead of print].
146. Hull J, Vervaart P, Grimwood K, et al. Pulmonary oxidative stress response in young children with cystic fibrosis. Thorax 1997;52(6):557–60.
147. Roum JH, Buhl R, McElvaney NG, et al. Systemic deficiency of glutathione in cystic fibrosis. J Appl Physiol 1993;75(6):2419–24.
148. Day BJ, van Heeckeren AM, Min E, et al. Role for cystic fibrosis transmembrane conductance regulator protein in a glutathione response to bronchopulmonary pseudomonas infection. Infect Immun 2004;72(4):2045–51.
149. Tirouvanziam R, Conrad CK, Bottiglieri T, et al. High-dose oral N-acetylcysteine, a glutathione prodrug, modulates inflammation in cystic fibrosis. Proc Natl Acad Sci U S A 2006;103(12):4628–33.
150. Griese M, Ramakers J, Krasselt A, et al. Improvement of alveolar glutathione and lung function but not oxidative state in cystic fibrosis. Am J Respir Crit Care Med 2004;169(7):822–8.
151. Hartl D, Starosta V, Maier K, et al. Inhaled glutathione decreases PGE2 and increases lymphocytes in cystic fibrosis lungs. Free Radic Biol Med 2005; 39(4):463–72.
152. Grasemann H, Gaston B, Fang K, et al. Decreased levels of nitrosothiols in the lower airways of patients with cystic fibrosis and normal pulmonary function. J Pediatr 1999;135(6):770–2.
153. Snyder AH, McPherson ME, Hunt JF, et al. Acute effects of aerosolized S-nitrosoglutathione in cystic fibrosis. Am J Respir Crit Care Med 2002;165(7):922–6.
154. Laguna TA, Sontag MK, Osberg I, et al. Decreased total serum coenzyme-Q10 concentrations: a longitudinal study in children with cystic fibrosis. J Pediatr 2008;153(3):402–7.
155. Oudshoorn JH, Lecluse AL, van den Berg R, et al. Decreased coenzyme Q10 concentration in plasma of children with cystic fibrosis. J Pediatr Gastroenterol Nutr 2006;43(5):646–50.
156. Nutritional management of cystic fibrosis. UK Cystic Fibrosis Trust Nutrition Working Group. Available at: www.cftrust.org.uk. 2002. Accessed July 28, 2009.