Journal of Pediatric Gastroenterology and Nutrition
35:246–259 © September 2002 Lippincott Williams & Wilkins, Inc., Philadelphia

Consensus Report on Nutrition for Pediatric Patients With Cystic Fibrosis

*Drucy Borowitz, *Robert D. Baker, and †Virginia Stallings

**Children's Hospital of Buffalo, Buffalo, New York, U.S.A.; Children's Hospital of Philadelphia For the Consensus Committee, Philadelphia, Pennsylvania, U.S.A.*

2001 CONSENSUS COMMITTEE MEMBERS

Laura K. Bachrach, M.D.
Robert J. Beall, Ph.D.
Preston W. Campbell, III, M.D.
Susan C. Casey, B.S., R.D.
Mitchell B. Cohen, M.D.
Mary Corey, Ph.D.
W. Hobart Davies, Ph.D.
Judy A. Fulton, R.D.
Richard J. Grand, M.D.
John E. Grunow, M.D.
Dana S. Hardin, M.D.
Lesles Hendeles, Pharm.D.
James E. Heubi, M.D.
Van S. Hubbard, M.D.
Hui-Chuan Kai, Ph.D.
Sheila Innis, Ph.D.
Elisabeth Luder, Ph.D., R.D.
Karen MacGuiness, R.D.
Richard K. Mathis, M.D.
Annie McKenna, M.S., R.D., C.N.S.
Antoinette Moran, M.D.
Laurie Moyer-Mileur, Ph.D., R.D.
Kimberly O. O'Brien, Ph.D.
Hebe Quinton, M.S.
Lynne M. Quittell, M.D.
Ross W. Shepherd, M.D., FRACP
Ronald J. Sokol, M.D.
Lori J. Stark, Ph.D.
John N. Udall, Jr., M.D., Ph.D.
Babette Zemel, Ph.D.

Address correspondence and requests for reprints to Robert D. Baker, MD, PhD, Digestive Disease and Nutrition Center, Children's Hospital of Buffalo, 219 Bryant St., Buffalo, NY 14222, U.S.A. (e-mail: rbaker@upa.chob.edu).

The Consensus Conference was co-sponsored by the Cystic Fibrosis Foundation and by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

INTRODUCTION

Patients with cystic fibrosis should have normal growth. Growth requires appropriate energy and nutrient intake, but gastrointestinal and pulmonary function and genetic potential are also important. Poor clinical outcomes are associated with undernutrition in patients with CF (1–6). The Cystic Fibrosis Foundation recognizes that attention to nutrition is an integral part of CF care. In March 2001 a Consensus Committee, co-sponsored by the Cystic Fibrosis Foundation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, met to review the literature and update a Consensus Conference Statement published in 1992 addressing these issues (7).

The CF care team should monitor growth, provide anticipatory counseling, and plan intervention strategies when patients are at risk for undernutrition or are diagnosed with nutritional failure. A registered dietitian must be a part of the team to provide the discipline-specific expertise needed for optimal nutritional management and may, along with other team members such as the physician, nurse, social worker or a psychologist, provide expertise concerning developmental and behavioral aspects of eating. Prevention and early intervention are most successful in combating nutritional failure. This document outlines the current recommendations of the Consensus Committee on how best to monitor growth and nutrition, strategies to prevent undernutrition, and interventions for patients with nutritional failure. It is based on the limited evidence available in the literature and also represents expert opinion. As with all such documents, these recommendations are likely to change as new data becomes available.

MONITORING GROWTH, BODY COMPOSITION, PUBERTAL AND BONE STATUS

Early detection of suboptimal growth allows for appropriate intervention and timely rehabilitation. Present

DOI: 10.1097/01.MPG.0000025580.85615.14

Cystic Fibrosis Foundation (CFF) guidelines suggest that patients be seen on a routine basis, every 3 months (8). Growth and nutritional status should be monitored at these intervals (Table 1).

There are three specific times when special attention should be focused on growth and nutritional status within the scope of usual clinical care. These are: (1) the first 12 months after the diagnosis of CF for each patient; (2) birth to 12 months of age for infants diagnosed prenatally or at birth, until a normal pattern of growth (head circumference, weight, and length) is clearly established; and (3) the peripubertal growth period (girls about 9 to 16, and boys about 12 to 18 years of age). By establishing a pattern of normal growth and development after the diagnosis of CF, patients enter mid-childhood and pubertal growth well nourished, and are more likely to continue this pattern of normal growth.

Surveillance of Growth and Body Composition

Accurate, sequential measurement, plotting and interpretation of head circumference, weight, length, and height are essential to the care of children with CF. Standard anthropometric measurement techniques are well described in the literature (9–11). Mid-arm circumference and triceps skinfold thickness measurements provide clinical information about lean body mass (muscle and organ) development and subcutaneous fat (energy) stores, respectively. Each center should select and maintain anthropometric instruments, establish a detailed measurement protocol, and train those responsible for obtaining anthropometric measurements. Each clinic should also have standard protocols for cleaning the instruments between patient assessments to protect against the spread of infectious agents.

Clinical Evaluation of Measures of Growth and Body Composition

Evaluation of Growth Measurements

Weight and length (measured supine) or height (measured standing), as well as head circumference in infants, should be monitored and analyzed as growth parameters. In 2000, new NCHS/CDC growth charts were distributed for plotting weight, head circumference, length, and height (CDC web site, http://www.cdc.gov/growthcharts to download charts). The percentiles for all growth measures are expanded, compared to the 1977 charts, with two new percentile curves (97th and 3rd) for more precise evaluation at the extremes of the growth distribution. In addition, charts are provided for body mass index (BMI $=$ (weight in kg)/(height in meters)^2) with percentiles for boys and girls, age 2 to 20 years. Reference values are available for tracking head circumference in children beyond 36 months of age (12).

The 2000 edition growth charts should be used for all CF clinical care, and have been used in calculation of the CFF Patient Registry data beginning with the 1999 annual report. For optimal care, it is suggested that patients less than 24 months of age have all previously collected growth data (weight, length, head circumference) com-

TABLE 1. *Nutritional assessment in routine CF center care*

	At diagnosis	Every 3 months birth to 24 months	Every three months	Annually
Head circumference	x[a]	x		
Weight (to 0.1 kg)	x	x	x	
Length (to 0.1 cm)	x	x		
Height (to 0.1 cm)	x		x	
Mid-arm circumference (to 0.1 cm)	x			x
Triceps skinfold (to 1.0 mm)	x[b]			x
Mid-arm muscle area, mm^2 (calculated from MAC and TSF)	x[b]			x
Mid-arm fat area, mm^2 (calculated from MAC and TSF)	x[b]			x
Biological parents height[c]	x			
Pubertal status, female				x[d]
Pubertal status, male				x[e]
24 hour diet recall				x
Nutritional supplement intake[f]				x
Anticipatory dietary and feeding behavior guidance		x	x[g]	x

[a] If less than 24 months of age at diagnosis;
[b] Only in patients over one year of age;
[c] Record in cm and gender-specific height percentile; note patient's target height percentile on all growth charts;
[d] Starting at age 9 years, annual pubertal self-assessment form (patients, or parent and patient) (Reference 25) or physician examination for breast and pubic hair Tanner stage determination; annual question as to menarchal status. Record month and year of menarche on all growth charts;
[e] Starting at age 10 years, annual pubertal self-assessment form (patients, or parent and patient) (Reference 25) or physician examination for genital development and pubic hair Tanner stage determination;
[f] A review of enzymes, vitamins, minerals, oral or enteral formulas, herbal, botanical and other CAM products;
[g] Routine surveillance may be done informally by other team members, but the annual assessment and q 3 monthly visits in the first two years of life and q3 monthly visits for patients at nutritional risk should be done by the Center Dietician.

pletely transferred to a 2000 edition growth chart. For patients older than 24 months, it is suggested that previously collected growth data be transferred to the 2000 growth charts for each six-month interval. Based upon clinical judgment of the pattern of growth and related clinical events (i.e., prolonged illness, use of a feeding tube, lung transplantation), more extensive growth data should be transferred to the 2000 edition growth chart.

One strong indicator of global nutritional sufficiency is if patients are growing in height to their full genetic potential (13). The genetic potential for height of each patient can be estimated by a variety of methods (14–16). This should be determined for each patient and the target height range (genetic potential related to biologic parental height) should be noted on the growth chart. Catch-up linear growth may take up to four years in children with CF diagnosed in infancy (17). A steady increase in percentile height towards the target height range indicates adequate nutritional status.

Evaluation of Weight for Height Proportion

Assessment of the weight for height proportion for an individual patient is of clinical importance. The 1992 CFF Consensus Report (7) contained some inconsistencies in how to use the recommended weight-for-height index. In practice, some CF Centers adopted the Moore modification (18) while others used the original McLaren and Read method (19). To standardize the approach to assessing relative proportion of weight for height, the committee now recommends that the term 'percent ideal body weight' (abbreviated as '%IBW') and the modification of Moore et al. be used. This recommendation will be followed in subsequent discussions (Fig. 1). Users of software that calculates %IBW must know what method the program employs, since not all programs use the Moore method. Although somewhat cumbersome to calculate, %IBW remains a very sensitive index of body weight allowing for gender, age, and height. Weight-for-height percentile from NCHS/CDC growth charts is less valuable because the age of the child is ignored.

Step 1: Plot the patient's height (length) on the growth chart and determine the height percentile. If less than the 3rd percentile, estimate the distance from the 3rd percentile as a fraction of the distance between the 3rd and 50th percentile. The same fraction of the 3rd to 50th percentile on the weight chart will be used to indicate the ideal weight below the 3rd. These estimates can be done by eye, or by using precise z-scores from a computer program.

Step 2: Determine the ideal body weight (The weight that corresponds to the patient's height percentile, e.g. for a 6 year old girl with a height on the 25th percentile, the ideal weight should be on the 25th percentile of the weight chart for a 6 year old girl).

Step 3: %IBW= (actual weight in kilograms /ideal body weight in kilograms) X 100.

From Reference 18.

FIG. 1. Calculation of percent ideal body weight (% IBW).

BMI is an estimate of adiposity, which should remain relatively constant throughout adulthood. However, BMI is not constant across the pediatric age range; therefore, BMI percentiles available on the 2000 CDC growth charts, rather than BMI, should be used to evaluate the pediatric patient. Guidelines for classifying underweight by BMI have been reported in the general population for adults but have not been validated in children with CF (20,21). Although the cut-off values for BMI percentiles that relate to health status are not yet well established, low BMI has been shown to be associated with increased mortality (22). Since children are growing in weight and stature, the Consensus Committee recommends that BMI percentile should be used for clinical evaluation. Just as with percentile height and weight charts, an individual BMI percentile value reflects genetic as well as health factors. Plotted sequential values indicate problems when the pattern varies from a consistent percentile. For now, it is suggested that both %IBW and BMI percentile be calculated and used for clinical care decisions. BMI percentiles are not available for children under age 2 years, so weight-for-length percentile should be used.

Evaluation of %IBW, BMI percentiles, and weight-for-length percentiles permits the identification of patients at risk for nutritional failure (Table 2). However, not all patients in the 'at risk' category will have nutritional insufficiency. Use of percentiles, by definition, only describes the distribution of growth in a population. Expertise will need to be used to determine who requires closer evaluation and follow-up to prevent nutritional failure. Patients who meet the definition of nutritional failure, as outlined in Table 2, should be evaluated and treated (see below).

Evaluation of Body Composition Measurements

The two body composition measurements, mid-arm circumference and triceps skinfold thickness, are translated to age- and gender-specific percentiles using reference data from Frisancho (23). Two additional values are calculated from the mid-arm circumference and triceps measurements, and provide more accurate assessments of muscle and fat stores. These are the mid-arm muscle area (mm^2) and mid-arm fat area (mm^2) with age and gender reference data also provided by Frisancho (23).

Clinical Evaluation of Pubertal Development

Pubertal development is often delayed in patients with CF. This delay is usually related to growth failure and poor nutritional status, rather than to a rare primary endocrine disorder. Progressing through pubertal development is an important component of physical growth as well as psychosocial health of the child and family. In

TABLE 2. *Definition of nutritional failure in patients with CF and those at risk*

Nutritional status	Length or height	Percentage IBW[1] All ages	Weight-for-length percentile[2] 0 to 2 years	BMI percentile[3] 2 to 20 years	Action
Acceptable	Normal growth	≥90%	>25th	>25th	Continue to monitor with usual care
At-risk[4]	Not at genetic potential	≥90%, with weight loss or weight plateau[5]	10 to 25th	10 to 25th	Consider nutritional and medical evaluation; some but not all patients in this category are at risk for nutritional failure
Nutritional failure	<5%ile	<90%	<10th	<10th	Treat nutritional failure

1. From Reference 18 and Reference 7.
2. From 2000 NCHS/CDC growth charts (weight-for-length) available for children, ages 0 to 2 years.
3. From 2000 NCHS/CDC growth chart, available for children and adolescents, ages 2 to 20 years.
4. Delayed puberty should also be considered a marker of patients at risk for nutritional failure (no breast development past age 13 in girls; no menarche by age 16 or more than 5 years after the start of breast development in girls; no testicular enlargement or genital changes by age 14 in boys).
5. Weight plateau is defined as no increase in weight for >3 months in a patient under 5 years of age, or no increase in weight for >6 months in a patient over 5 years of age.

addition, studies now show that the period of pubertal growth is also very important to achieving peak bone mass and adult bone health (24). A standardized method of self-assessment (child or child/parent) (25) or physical examination (trained physician or registered nurse) (26) should be completed at least annually, in girls beginning at age 9 years and boys at age 10. Delayed puberty should be considered a marker of nutritional failure (Table 2).

CLINICAL EVALUATION OF BONE HEALTH

Bone health is of increasing interest for patients with CF, as several studies have demonstrated bone fragility in children and adults with CF (27,28). Peak bone mass is one of the major determinants of life-long bone health and is attained by early adulthood (29–31). CF with pancreatic insufficiency poses many potential risk factors for poor bone health: failure to thrive, delayed or truncated pubertal development, malabsorption of calcium, magnesium, and vitamins D and K, hepatobiliary disease, and reduced weight-bearing physical activity. Chronic use of corticosteroid medications for lung disease is also a risk factor for poor bone health, and may decrease calcium absorption and suppress linear growth (32).

Bone health can be evaluated by history (e.g., atraumatic bone fracture), physical examination (poor growth, back pain), and by radiologic and laboratory assessment. Plain radiography films (chest, long bones) that demonstrate osteopenia are usually indicative of significant loss of bone mass or lack of normal accretion of bone mass. Conventional x-ray is not nearly as sensitive or quantitative as dual energy x-ray absorptiometry (DEXA) using an age- and gender-adjusted standard deviation score (z-score) for the lumbar spine (L1–4 or L2–4). Further adjustments for small bone size and/or delayed skeletal maturation may be required to avoid over-diagnosis of low bone mass, although currently there are no standard methods for these adjustments. Comparison of scans from children or adolescents with adult reference data (T-score) is not appropriate.

Children 8 years old and older who have one of the following risk criteria for poor bone health should have an assessment of bone mass by lumbar spine DEXA: candidate for organ transplantation, post-organ transplantation, end-stage lung disease, bone fracture associated with low-impact activity (i.e., fracture with a fall from standing height), chronic use of corticosteroid medication, delayed pubertal development, and nutritional failure. In addition to the DEXA, children at risk for poor bone health should have annual serum calcium, phosphorous, intact parathyroid hormone measured in addition to routine annual 25-hydroxyvitamin D level. Also, the dietary intake of calcium and vitamin D should be determined by diet history. Abnormal blood values or suboptimal dietary intake should be corrected by treatment.

Current treatment of osteopenia or osteoporosis in children with CF is usually limited to general health measures, including optimizing growth by supplying adequate calories, general nutrition by ensuring sufficient vitamin D and K intake to normalize blood levels, encouraging calcium intake that meets the recommendations for age (33), and by fostering weight-bearing physical activity as tolerated. Antiresorptive drug therapy remains experimental, but may be used in lung transplant patients and may ultimately prove appropriate for patients with a history of low-impact bone fractures. Referral to a physician specializing in treating bone health in children may be considered.

NUTRITION MANAGEMENT IN THE WELL CHILD

Issues Related to Pancreatic Insufficiency

Identifying Pancreatic Insufficiency

Eighty-five to 90% of patients with CF have pancreatic insufficiency (PI) (34). The majority of pancreatic

function must be lost before symptoms of PI are apparent (35). PI leads to malabsorption of dietary fat, protein, and other nutrients. Pancreatic functional status is a strong predictor of long-term outcome (36) and has a direct influence on nutritional status; therefore, knowing the pancreatic phenotype is useful not only in nutritional management but as a prognosticator. Specific CFTR mutations are associated with pancreatic sufficiency in a dominant fashion (see Table 3). Possessing an allele from this group offers protection even in combination with an allele normally associated with PI (37).

When the diagnosis of CF has been established, PI is often inferred by clinical signs and symptoms such as: frequent, malodorous, greasy stools, the presence of meconium ileus, or distal intestinal obstruction syndrome. Tests to document PI include: (1) duodenal intubation with stimulation; (2) 72-hour fecal fat balance study; (3) immunoreactive trypsinogen after 8 years of age; and (4) other markers as they become more widely available, such as fecal elastase-1 and fecal chymotrypsin determinations (38). Indirect tests to infer PI include low serum fat-soluble vitamins and/or low serum beta-carotene (after the introduction of fruits and vegetables). It is important to assess the pancreatic function of patients as soon as the diagnosis of CF is made. Steatorrhea may be the result of other conditions. When PI is present, enzyme, and vitamin therapy (Table 4) as well as proactive nutritional management should be started.

Some patients whose tests initially indicate that they are pancreatic sufficient (PS) become PI. PS patients should be reevaluated annually for the conversion to PI, especially if genetic testing reveals two mutations that are generally associated with PI. This evaluation can consist of monitoring growth, nutrition, and stool pattern; one or more of the tests listed above for assessing pancreatic function may be needed for more objective evidence.

Recommendation for Pancreatic Enzyme Replacement Therapy

Pancreatic enzyme replacement therapy is initiated once PI has been identified. Enzymes are given with all foods and milk products including predigested formulas and breast milk. Medium chain triglycerides (MCT) require less lipase activity than long-chain fats for efficient absorption, although lipase is still needed (39). Microsphere or microtablet preparations are preferable to powders because the acid-resistant enteric coating prevents acid-inactivation of the enzymes, and are not associated with mouth and/or perianal excoriation. Decreased pancreatic bicarbonate secretion combined with gastric acid may cause the duodenum and proximal jejunum to remain acidic, preventing dissolution of the protective coating until the capsules have bypassed a significant amount of intestinal absorptive surface. This can be treated by the administration of a histamine-2 receptor blocker or a proton pump inhibitor (40,41). Enzymes work best when taken before each meal and snack. For prolonged meal events, such as at a buffet or party, the enzymes may be more effective if distributed throughout the meal. Parents and adolescent should learn to adjust enzyme dosage according to the anticipated amount of fat in the meal or snack based on guidance from their CF team. Schools and caretakers should be aware of the need for enzymes with all meals and snacks.

TABLE 3. *Pancreatic function and mutations*

Pancreatic-sufficient dominant CF mutations	Variable pancreatic-sufficient CF mutations
G551S	G85E
P574H	R347P
R117H	3849 + 10kb C → T
R334W	A455E
R347H	2789 5G → A
R352Q	
T3381	

Generic enzymes are not bio-equivalent to proprietary enzymes (42). Therefore it is recommended that only proprietary enzymes be prescribed and that the prescription be marked 'no substitution,' or an equivalent statement.

The adequacy of enzyme therapy can be assessed subjectively by following growth parameters and stool patterns. At present the best objective test available is a 72-hour fecal fat collection with calculation of a coefficient of fat absorption. Infants taking MCT-enriched formulas or patients receiving MCT-containing enteral formulas must have stool analyzed for fat using the Jeejeebhoy method (43) to avoid false negative results. A variety of newer methods are being developed to determine the adequacy of enzyme therapy, but are not yet available for clinical use (44). This is an important research area. Tests such as fecal elastase-1 and stool chymotrypsin are measures of pancreatic function but do not establish the adequacy of enzyme replacement.

A more complete discussion of pancreatic enzyme replacement therapy can be found in the report of the Consensus Conference on Enzyme Therapy and Fibrosing Colonopathy (45). To avoid fibrosing colonopathy, it is recommended that enzyme doses should be less than 2500 lipase units/kg per meal or less than 4000 lipase units/gram fat per day (46).

Developmental Approach to Nutritional Anticipatory Guidance

Infants (First Year of Life)

Breast-feeding is recommended for most infants as the primary source of nutrition for the first year of life. Proprietary formulas can also be used. Intolerance to cow's

TABLE 4. *Recommendations for vitamin supplementation In addition to a standard, age appropriate dose of non-fat-soluble multivitamins, the following should be given:*

	Individual vitamin daily supplementation			
	Vitamin A (IU)	Vitamin E (IU)	Vitamin D (IU)	Vitamin K (mg)
0–12 months	1500	40–50	400	0.3–0.5*
1–3 years	5000	80–150	400–800	0.3–0.5*
4–8 years	5,000–10,0000	100–200	400–800	0.3–0.5*
>8 years	10,000	200–400	400–800	0.3–0.5*

* Currently, commercially available products do not have ideal doses for supplementation. In a recent review, no adverse effects have been reported at any dosage level of Vitamin K (Reference 110). Clinicians should try to follow these recommendations as closely as possible until better dosage forms are available. Prothrombin time or, ideally, PIVKA-II levels should be checked in patients with liver disease, and vitamin K dose titrated as indicated.

milk, either from allergy or lactose intolerance, is no more common in patients with CF than in the general population. Often, a caloric density greater than the standard 20 kcal/ounce may be needed and can be achieved by fortifying breast milk, by concentrating formula, or by the addition of fat and/or carbohydrate. Breast or formula feeding should continue for the first 12 months of life. Thereafter, whole milk can be used in the thriving child. Solid foods should be added at 4 to 6 months developmental age according to the recommendations of the American Academy of Pediatrics. Infant cereal should be prepared with formula or breast milk, not water or juice.

Sources of fluoride and iron should be identified within the first year, in addition to the vitamin supplementation recommended for children with CF (Table 4). Supplemental fluoride and iron need to be given if the dietary intake is inadequate (47,48). Hyponatremic alkalosis may occur in the breast or formula fed infant with CF. Supplementation with sodium chloride, especially during the summer is necessary (see below).

For infants who are taking solids but not achieving their expected rate of growth, additional calories can be added to infant cereal with the addition of carbohydrate polymers (e.g., Polycose®, Ross Laboratories Division, Abbott Labs, Columbus, OH)) and/or fats such as vegetable oil, Microlipid®, (Mead Johnson, Evansville, IN) or MCT oil. As infants are introduced to table foods, it is important that families understand the concept that children with CF should eat a balanced diet that is moderate to high in fat and protein. Parents and caregivers should be aware that this advice is counter to the usual nutritional advice for children without CF.

Toddlers to Preschool Age (1–4 Years)

At this age, dietary intake and degree of physical activity vary from day to day. Routinely adding calories to table foods may help with maintaining growth at this stage. The family should buy whole milk for the child with CF and lower fat milk for other family members over two years of age. Parents should avoid giving their children with CF low fat or low calorie foods. During the second year of life children establish self-feeding skills, food preferences, and dietary habits. Mealtime is a social event as well as a nutritional one. Dietitians caring for patients with CF should inquire about feeding behaviors to promote positive interactions and to prevent negative behaviors before they become entrenched. Grazing behavior should be discouraged.

School Age (5–10 Years)

This is a high-risk period for decreased rate of growth in children with CF (49,50). Participation in activities leading to limited time for snacks and enzyme adherence, taste fatigue, and progression of disease may be responsible for this decrease in growth rate. Behavioral interventions should be considered in this age group if problematic mealtime behaviors are identified. School-age children must have a basic knowledge of physiology and practical aspects of enzyme therapy.

Adolescence (11–18 Years)

This stage is associated with high nutrient requirements due to accelerated growth, pubertal development, and high levels of physical activity. CF adolescent development and behavior reflect the general population. Pulmonary infections are more common in this period, also increasing nutritional needs. Females are at greater risk for nutritional failure (51). This is an age when confounding factors, such as CF-related diabetes or liver disease, may complicate nutrition management. Growth failure and pubertal delays may occur and come at a time of social pressure and psychosocial stress. Nutritional counseling will be more effective if directed toward the patient as well as toward the parent. Teenagers may be more receptive to efforts to improve muscular strength and body image as a justification for better nutrition than stressing weight gain and improved disease status.

Recommendations for Energy Intake and Specific Nutrients

Energy Intake

Optimal dietary intake is an essential component of nutritional care of the patient with CF especially in the presence of pancreatic insufficiency. Patients with CF often require a greater fat intake (35 to 40% of calories) than that recommended for the general population ($\leq$30%). Energy intake should be evaluated based on the pattern of weight gain and of fat stores. There is no perfect method to estimate the caloric needs of an indi-

vidual with CF. The desired clinical outcome is a steady rate of weight gain in growing children.

Fat-Soluble Vitamins and Beta Carotene

Fat malabsorption can lead to the loss of vitamins that are aggregated with fat. Patients with CF who are adequately treated with pancreatic enzymes continue to malabsorb fat-soluble vitamins. Bile acids also are necessary for absorption of fat and fat-soluble vitamins; patients with CF have malabsorption of bile acids as well as pancreatic dysfunction (52). Patients with CF who have liver disease or interruption of the enterohepatic bile acid circulation thus are at even higher risk for fat-soluble vitamin malabsorption. There is ample evidence that patients with CF become depleted of fatty substances (53–57). Recommendations for surveillance and replacement of these substances are given in Tables 5 and 4.

Beta-Carotene Beta-carotene is a precursor of vitamin A and may also function as an antioxidant. It is uncertain whether a beta-carotene deficiency state exists in patients with CF or not. A number of studies have documented low serum levels of beta-carotene in patients with CF that, with oral supplementation, can be corrected (53,58,59). One randomized study showed a decreased number of days on antibiotics for patients taking beta-carotene, suggesting that it may play a physiologic role (59). Further evidence for a clinical deficiency state is lacking.

Vitamin A Vitamin A is important for vision, epithelial cell integrity, epithelial proliferation, and immunity. Pancreatic lipase is required to digest retinyl esters before absorption. In cross-sectional studies between 15 and 40% of CF patients have been found to be vitamin A deficient (54,60,61). In one study, 18% of adult CF patients were found to have deficits in dark field adaptation (62). The combination of these studies suggests that Vitamin A deficiency in CF is common. Vitamin A is a negative acute phase reactant, so levels measured during acute illnesses may yield misleadingly low results (63). Thus, surveillance levels should not be drawn at the time of admission to the hospital for illness.

Vitamin D Vitamin D functions to increase calcium absorption. Vitamin D nutriture takes on added importance because of the prevalence of osteoporosis and bone fractures among patients with CF (64). Ten to forty percent of patients with CF have been demonstrated to be deficient in vitamin D (55). Older children and adults and those residing in northern latitudes are more likely to have inadequate 25-hydroxy vitamin D levels, because of limited exposure to sunlight.

Vitamin E Vitamin E (alpha tocopherol) is an antioxidant. Deficiency states lead to hemolytic anemia, neuromuscular degeneration, as well as retinal and cognitive deficits. Vitamin E has been reported to be low in patients with CF, even in those taking pancreatic enzymes and multivitamins, and symptomatic deficiency states have been reported (65,66). Five to ten percent of CF patients continue to have low serum vitamin E levels despite supplementation (56).

Vitamin K (Phylloquinone, Menaquinone) Vitamin K functions in the biosynthesis of clotting factors and with osteocalcin as well as in GLA protein hydroxylation. Since measurement of serum vitamin K levels is not practical, plasma prothrombin concentration (PT) has been used as a surrogate. Although it is not widely available, PIVKA-II (Proteins Induced by Vitamin K Absence or Antagonism) is a more sensitive measure of vitamin K

TABLE 5. *Laboratory monitoring of nutritional status*

	How often to monitor			
	At diagnosis	Annually	Other	Tests
Beta carotene			At physician's discretion	Serum levels
Vitamin A	x*	x		Vitamin A (retinol)
Vitamin D	x*	x		25-OH-D
Vitamin E	x*	x		α-tocopherol
Vitamin K	x*		If patient has hemoptysis or hematemesis; in patients with liver disease	PIVKA-II (preferably) or prothromin time
Essential fatty acids			Consider checking in infants or those with FTT	Triene:tetraene
Calcium/bone status			>age 8 years if risk factors are present (see text)	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

* Patients diagnosed by neonatal screening do not need these measured.

adequacy. Insufficiency of vitamin K leads to the formation of under γ-carboxylated vitamin K-dependent clotting factors. PIVKA-II will detect changes of a few ng/ml while PT detects changes of 100 μg/ml. Some authors suggested that vitamin K deficiency was uncommon, while others, using the more sensitive PIVKA-II, found it to be very common, even if enzymes and multivitamins are given (55,57,66,67). Colonic bacteria are a source of vitamin K. Disruption of the enteric flora by antibiotic use can reduce vitamin K levels. In a study of adults with CF who were taking oral antibiotics, vitamin K at doses of 5mg four times a week was not sufficient to correct PIVKA-II levels. This study suggests that previous recommendations for vitamin K replacement during antibiotic therapy may be inadequate (66).

Essential Fatty Acids and DHA

Biochemical essential fatty acid deficiency (EFAD) is common in patients with CF, and can occasionally be seen in PS patients as well as in those who are PI (68–71). However, clinical signs and symptoms are rare, although EFAD should be considered in young infants with failure to thrive. The triene:tetraene ratio falls in patients with EFAD. Essential fatty acids are polyunsaturated fats that can be metabolized to linoleic (n-6 series) and alpha-linolenic acid (n-3 series). Linoleic acid is further metabolized to arachidonic acid (AA), and alpha-linoleinic acid is metabolized to docosohexaenoic acid (DHA). DHA downregulates AA incorporation into phospholipid membranes. Failure of DHA to limit AA incorporation may be a factor in the increased AA seen in bronchoalveolar lavage fluid in patients with CF. There has been speculation that abnormal fatty acid metabolism is a primary problem in CF (i.e., is not secondary to fat malabsorption) (72). Whether DHA supplementation is warranted in patients with CF is the subject of careful research; no recommendations can be made at the present time. Vegetable oils such as flax, canola and soy, and cold-water marine fish are rich in linolenic acid, are a good source of energy and can be recommended. Human breast milk contains DHA and should be encouraged for infants.

Minerals and Electrolytes

Calcium Recently, dietary calcium recommendations for the general population have been revised upward (33). There has also been an increased awareness of the high prevalence of osteopenia, osteoporosis, and an increased fracture risk in children and adults with CF. Several studies have indicated that calcium insufficiency and low bone mass are major issues of concern even in the pediatric CF population (28,73–75). To maximize skeletal accretion of calcium in children and adolescents, intake should, at a minimum, achieve levels specified by the 1997 IOM recommendations.

Iron Iron deficiency is an issue of concern for children with CF (76–78). Ferritin is frequently used as an index of iron status. However, ferritin is an acute phase reactant and may be artificially elevated in patients with CF due to concurrent inflammation. Serum transferrin receptors are a more sensitive indicator of iron deficiency because they are not affected by inflammation, but at present, this test is not available commercially (79). Until better tests are available, it is recommended that iron status be monitored yearly in children and adolescents with CF by checking hemoglobin and hematocrit.

Zinc Recent stable isotope studies have reported increased endogenous fecal zinc losses and decreased zinc absorption in children and infants with CF (80,81). Zinc deficiency in CF is difficult to characterize because zinc deficiency may be present when plasma zinc is in the normal range. Empiric zinc supplementation as a treatment trial for a period of six months can be considered for CF patients who are failing to thrive or have short stature. Zinc deficiency is known to affect vitamin A status, so zinc supplementation is also reasonable in CF patients with suboptimal vitamin A status or in those who report night blindness that does not respond to vitamin A therapy alone (54).

Sodium Infants and children with CF are at risk of hyponatremia because of salt loss through the skin. The evidence in infants is limited to case reports (82,83), while sodium loss in older patients with CF has been studied in more detail (84). Patients with CF are advised to take in a high salt diet. This recommendation should be emphasized during the summer months and for those who live in hot climates. Infants without CF require 2–4 mEq/kg/d of sodium; infants with CF likely are at the upper end of this range when not exposed to heat stress. Before the introduction of complementary foods or when exposed to heat stress, babies with CF should have supplemental sodium. Historically, sodium supplements have been given using 1/8 tsp table salt (which contains approximately 11 mEq sodium). This method has the disadvantage of being imprecise and has the potential for mistakes. Sodium chloride solutions are available through pharmacies and can be dispensed more accurately.

Complementary and Alternative Medicine (CAM)

It is estimated that between 33 and 66% of CF patients have used non-traditional medicine (85,86). Interestingly, 33 to 100% of these patients report achieving benefit from these therapies. Use of herbal or dietary therapies is lower, in the range of 11 to 28%. CAM products are problematic for two reasons. First, no proof of safety or efficacy is required by U.S. law and second, there is no assurance of purity, potency, or quality.

Patients with CF and their parents may be reluctant to discuss non-traditional therapies with medical team. The American Academy of Pediatrics' Committee on Children with Disabilities published guidelines on CAM therapy that state: "To best serve the interest of children, it is important to maintain a scientific perspective, provide balanced advice about treatment options, guard against bias, and to establish and maintain a trusting relationship with families" (87). It is important to ask patients with CF and their parents about CAM in a non-judgmental way.

EVALUATION OF PATIENTS WITH NUTRITIONAL FAILURE AND THOSE AT RISK

Definition of Nutritional Failure and Patients at Risk

Criteria for considering patients to have nutritional failure and to be at risk for nutritional failure are given in Table 2. When poor growth is identified, patients should be seen more frequently than the every three-month Center visits outlined in the Practice Guidelines for routine surveillance. Infants should be seen every two to four weeks, and children over age two years should be seen every four to six weeks. These visits should include medical, behavioral, and nutritional assessment, education and intervention as outlined in Figure 2. Nutrition intervention should aim at achieving the patient's target goal for both weight-for-height proportion and genetic height potential.

Evaluation of Co-Morbid Medical Conditions

Medical as well as nutritional and behavioral factors should always be considered in the patient who fails to gain weight. If pulmonary or sinus disease are active, these should be treated. Gastroesophageal reflux disease (GERD) occurs with increased frequency in patients with CF of all ages, and can cause both pulmonary symptoms and poor growth (88,89). An extensive review of the literature and recommendations for diagnosis and treatment of GERD in infants and children has recently been published (90). CF related diabetes (CFRD) with or without fasting hyperglycemia can cause poor growth. Insulinopenia causes protein catabolism (91). An oral glucose tolerance test should be considered strongly in all patients with poor growth. The reader is referred to the recent Consensus Conference for management of CFRD (92). Non-pancreatic causes of malabsorption may also contribute to poor growth. These include CF-related hepatobiliary disease (93), infectious enteritis, bacterial overgrowth of the small intestine, or intestinal mucosal problems such as Crohn's or celiac disease. Intestinal resection with short bowel syndrome, which may occur following surgery for meconium ileus, can worsen fat malabsorption and result in poor essential fatty acid status and poor growth (94). Fibrosing colonopathy should be considered in patients who have received pancreatic enzyme supplements at doses greater than 2,500 lipase units/kg/meal (45). Referral to a gastroenterologist may be warranted for patients with persistent poor growth.

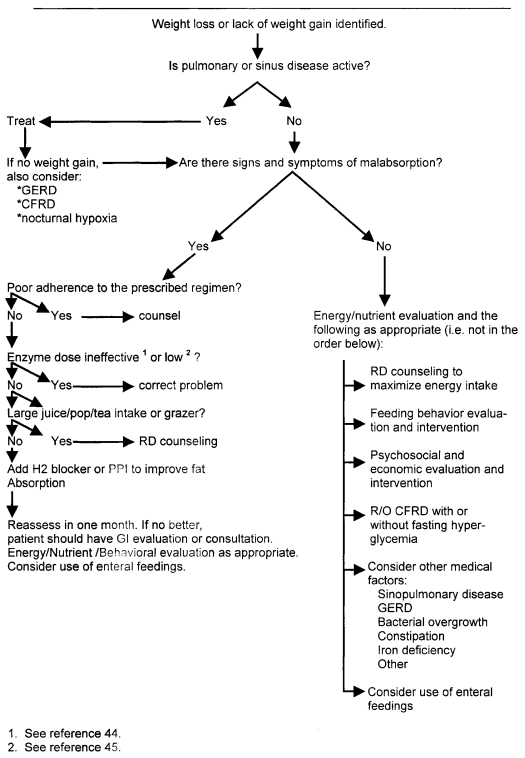

FIG. 2. Algorithm for CF patients with weight loss or lack of weight gain.

An important and easily treatable cause of poor growth and nutritional status in the patient with PI is ineffective pancreatic enzyme replacement therapy. In addition, inactivation of enzymes by an acidic duodenal environment may render even an appropriate dose ineffective.

Behavioral Evaluation

Presence of ineffective feeding behaviors and parenting strategies should be assessed early in the evaluation of patients with nutritional failure. The Behavioral Pediatrics Feeding Assessment Scale is a self-reported measure of mealtime problems (95). It is easy to use and appears to have adequate psychometric properties to be used clinically to identify problem behaviors that can be addressed to improve caloric intake. Research on eating in adolescents with CF has primarily focused on assessment of eating disorders or disturbances of body image, and no excess of these problems has been identified. However, concomitant anorexia nervosa should be con-

sidered in the adolescent with CF with very low body weight.

Dietary Evaluation

Dietary intake can be difficult to assess if patients are eating breakfast and/or lunch at school, meals are being served by daycare centers, sitters or relatives, or if the parents are working alternate shifts and meals are not eaten together. Specific questions should be asked about the volume of juice, flavored sugar drinks and carbonated beverages ingested, as well as the fat content and volume of milk. Parents should be questioned about fat-free or low-fat foods, which may be used "on the run" when enzymes are unavailable. Meals may be skipped altogether if the child is too rushed to eat breakfast, dislikes school lunches, or has an activity schedule which interferes with dinner. A 24-hour dietary recall provides a qualitative assessment of dietary patterns and is easily obtained in the office setting. A prospective 3 to 5 day diet record must be collected for any quantitative assessment of energy and nutrient intake. Medical factors such as iron deficiency or constipation should be considered in children with poor appetites.

Interventions for Patients With Nutritional Failure

Behavioral Intervention

If problematic mealtime behaviors as described under behavioral assessment are identified, behavioral intervention may be used in conjunction with nutritional intervention to improve oral intake. Behavioral interventions have been demonstrated to be effective in changing feeding dynamics for children ages 3 to 12 years and their parents in a research setting (96) and can be used in the clinical setting. The first behavioral strategy is to *gradually* increase calories by working on one meal at a time. A second strategy involves teaching parents alternative ways of responding to their child who eats slowly or negotiates what he or she will eat. A third strategy is to identify appropriate rewards for eating the expected amount of food at each meal. Referral for more in-depth behavioral therapy should be considered.

Dietary Interventions

Oral Supplements Generally, nutritional interventions start with addition of high-calorie foods to the patient's regular diet and use of nutritional energy supplements. Positive weight gain was demonstrated by one randomized study and one case-controlled study of nutritional counseling and homemade high-calorie foods (97,98). Two studies using commercially available supplements failed to improve nutritional status (99,100). Use of energy supplements is warranted, but surveillance is necessary to assure that they are not used as substitutes for normal food intake. The convenience of pre-packaged supplements may be useful for patients with busy schedules.

Enteral Feedings

Introduction to Family and Initiation Supplemental enteral feedings should be started when oral supplementation fails to result in weight gain. The purpose and goals of enteral feedings should be explained to the patient and family, and their acceptance and commitment to this intervention should be realistically assessed. Enteral feedings should be presented as a positive treatment, not as a threat or "the beginning of the end". Likewise, enteral feedings should be presented as a supportive therapy to improve quality of life and outcome. A possible way of assuring that families and patients understand this concept is to introduce the idea of enteral feeds at diagnosis or early in the course of CF, before nutritional failure is present. Enteral feeds should be presented as one of many treatment modalities to improve nutritional status and quality of life. The family should be provided with concrete information on the types of feeding tubes and formulas and how feeding systems work.

Since no good data exist to demonstrate the superiority of one type of enteral access over another, the choice of tube and technique for its placement (nasogastric, orogastric, gastrostomy, or jejunostomy) should be based on the experience of the Center. Some clinicians believe that the presence and/or severity of GERD should be assessed before initiation of enteral feedings, and if severe GERD is present, an antireflux procedure should be performed at the time of gastrostomy placement. Further research is needed to clarify the risks and benefits of this approach. Pulmonary health should be maximized before placement of all permanent tubes, and a plan for management of postoperative pain should be made before the procedure.

Formulas and Caloric Goals Standard (complete protein, long-chain fat) formulas typically are well tolerated. Calorically dense formulas (1.5–2.0 kcal/cc) usually are necessary for provision of adequate calories. The data are unclear as to whether formulas with medium-chain triglycerides are beneficial. Some practitioners find semi-elemental formulas helpful in patients who have excessive anorexia, bloating or nausea. Nocturnal infusion is encouraged to promote normal eating patterns during the day. Initially, 30 to 50% of estimated energy requirements should be provided overnight. Anecdotally, a total daily caloric goal of 120 to 150 kcal/kg/d may be needed in infants to achieve catch-up growth and promote optimal lung growth. The amount of calories delivered should then be titrated based on the rate of weight gain, fat stores, and growth. Very low-fat, elemental formulas may be used without enzyme supplements for patient who have endotracheal tubes in place and should be given by continuous infusion to maximize absorption.

Use of Enzymes With Enteral Feedings There are inadequate data on the appropriate dosing of pancreatic enzymes with overnight enteral feedings. One study found that complete formula with enzymes given before and after feedings and semi-elemental (hydrolyzed protein, medium chain triglyceride-enriched) formula given without enzymes, were equally well absorbed, although there was a trend towards less absorption of long chain fat and protein in the semi-elemental formula group (101). One study indicated that enzyme replacement improved fat absorption in infants receiving semi-elemental formulas (102). Another study of three formulas containing 0, 32, and 58% of calories as fat demonstrated 82 to 85% fat absorption when the usual mealtime dose of enzymes was given orally both before and mid-way through 8-hour nocturnal enteral feedings (103). The Consensus Committee recommends that pancreatic enzyme supplements be taken orally in the usual pre-meal dose before all nocturnal enteral feedings (with the exception of very low-fat, elemental formulas, as above). Additional doses may need to be given mid-way through or at the end of a feeding. Further research is needed to define the optimal method to provide pancreatic enzyme supplementation with enteral feedings.

Complications Complications may be associated with enteral feedings. Patients on enteral feedings should be monitored for carbohydrate intolerance. Once the full caloric goal has been achieved, blood sugars should be checked two to three hours into the feeding and at the end of the feeding on two separate nights. Insulin should be added if these blood sugars are greater than 180 mg/dl. This schedule of blood sugar monitoring should be repeated when a patient is ill, receiving steroids, or if the patient is not gaining weight. Patients with permanent feeding tubes should have their skin evaluated for local breakdown. Patients with excessive bloating may benefit from the addition of pro-kinetic agents or use of a semi-elemental formula.

Anabolic Agents

Insulin promotes anabolism as well as lowering blood sugar. Proteolysis is higher in patients with CF than controls, but those with CF exhibit resistance to the anabolic effects of insulin (104). Insulin therapy improves weight in patients with CFRD and fasting hyperglycemia (105). It is unknown whether insulin therapy improves weight and muscle mass in malnourished patients who have CFRD without fasting hyperglycemia, but treatment of these patients with insulin should be considered on a case-by-case basis. One group of children treated with growth hormone had increased height and weight velocity, lean body mass, and pulmonary function and had decreased hospitalizations (106). However, since height and weight increased proportionately, treated patients remained significantly underweight at the end of one year of treatment, suggesting that this expensive intervention is not a replacement for nutritional intervention. Growth hormone can also reverse protein catabolism and decrease circulating inflammatory cytokines (107). Longitudinal studies are needed to determine if the improvements are sustained. There may be a role for growth hormone therapy in selected children with CF. Several small studies have demonstrated increased appetite and weight gain in patients treated with megestrol acetate (108–110), although side effects such as adrenal suppression, insulin resistance, development of Cushingoid facies, insomnia, hyperactivity, and hypertension have been noted. Improvements do not appear to be sustained after the drug is discontinued. Until more data become available that show the benefits outweigh the risks, anabolic agents cannot be recommended for routine use in CF.

CONCLUSION

Our aim is to have every child with CF achieve normal growth and development. This requires regular and accurate surveillance, adequate calories and nutrients, and a plan for prompt intervention when growth is suboptimal. This is best accomplished with a multidisciplinary team approach at an accredited CF Center. This document is intended to present our best recommendations based on current knowledge. However, cystic fibrosis and nutrition research is needed in many areas before guidelines can be made based on evidence and not consensus opinion.

REFERENCES

1. Kraemer R, Rudeberg A, Hadom B, et al. Relative underweight in cystic fibrosis and its prognostic value. *Acta Paediatr Scand* 1978;67:33–7.
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: 588–91.
3. Kerem E, Reisman J, Corey M, Canny GJ, et al. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992;326: 1187–91.
4. Dalzell AM, Shepherd RW, Dean SB, et al. Nutritional rehabilitation in cystic fibrosis: a 5 year follow-up study. *J Pediatr Gastroenterol Nutr* 1992;15:141–145.
5. Pencharz PB, Durie PR. Nutritional management of cystic fibrosis. *Ann Rev Nutr* 1993;13:111–36.
6. Beker LT, Russek-Cohen E, Fink RJ. Stature as a prognostic factor in cystic fibrosis survival. *J Am Diet Assoc* 2001;101: 438–42.
7. Ramsey BW, Farrell PM, Pencharz P, Consensus Committee. Nutritional assessment and management in cystic fibrosis: a consensus report. *Am J Clin Nutr* 1992;55:108–16.
8. Clinical Practice Guidelines for Cystic Fibrosis, 1997; Cystic Fibrosis Foundation, Bethesda, MD.
9. Gordon CC, Chumlea WC, Roche AF. Stature, recumbent length and weight. In: Lohman TG, Roche AF, Martorell R, eds. Anthropometric standardization reference manual. Champaign IL: Human Kinetics Books, 1988:3–8.

10. Callaway CW, Chumlea WC, Buchard C. et al. Circumferences. In: Lohman TG, Roche AF, Martorell R, eds. Anthropometric standardization reference manual. Champaign IL: Human Kinetics Books, 1988:51–52.
11. Harrison GG, Buskirk ER, Carter JEL, et al. Skinfold Thicknesses and measurement technique. In: Lohman TG, Roche AF, Martorell R, eds. Anthropometric standardization reference manual. Champaign IL: Human Kinetics Books, 1988:56–57.
12. Roche, AF, Mujherjee D, Guo S, et al. Head circumference reference data: birth to 18 years. *Pediatrics* 1987;79:706–12.
13. Wright CM, Cheetham TD. The strengths and limitations of parental heights as a predictor of attained height. *Arch Dis Child* 1999;81:257–60.
14. Garn SM, Rohman CG. Interaction of nutrition and genetics in the timing of growth and development. *Pediatr Clin N Am* 1966;13: 353–80.
15. Himes JH, Roche AF, Thissen D, et al. Parent-specific adjustment for evaluation of recumbent length and stature of children. *Pediatrics* 1985;75:304–13.
16. Falkner F, Tanner JM, eds. Human Growth, second edition, Vol 3, pp 104–107, New York, Plenum Press 1986.
17. Farrell PM, Kosorok MR, Rock MJ, et al. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. *Pediatrics* 2001;107:1–13.
18. Moore BJ, Durie PR, Forstner GG, et al. The assessment of nutritional status in children. *Nutr Res* 1985;57:97–99.
19. McLaren DS, Read WW. Weight/length classification of nutritional status. Lancet 1975;2:219–21.
20. U.S. Department of Agriculture, Agriculture Research Service Dietary Guideline Advisory Committee. Report of the Dietary Guidelines for Americans. 1995, to the Secretary of Health and Human Services and the Secretary of Agriculture, Beltsville, MD: USDA, 1995.
21. World Health Organization. Diet, nutrition, and the prevention of chronic diseases: Report of a WHO study group. Geneva: WHO Technical Report Series: 1990; no. 797:69–75.
22. Troiano RP, Frongillo EA, Sobal J, et al. The relationship between body weight and mortality: a quantitative analysis of combine information from existing studies. *Int J Obes* 1996;20: 63–75.
23. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr* 1981;34: 2540–45.
24. Bailey DA, McKaym HA, Mirwald RL, et al. A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: the University of Saskatchewan bone mineral accrual study. *J Bone Miner Res* 1999;14:1672–79.
25. Morris NM, Udry JR. Validation of a self-administered instrument to assess stage of adolescent development. *J Youth & Adolesc* 1980;9:271–80.
26. Tanner JM. Growth at Adolescence, 2nd edition. Oxford: Blackwell Scientific Pub, 1962.
27. Henderson RC, Madsen CD. Bone density in children and adolescents with cystic fibrosis. *J Pediatr* 1996;128:28–34.
28. Bhudhikanok GS, Wang M-C, Marcus R, et al. Bone acquisition and loss in children and adults with cystic fibrosis: a longitudinal study. *J Pediatr* 1998;133:18–27.
29. Bachrach LK. Acquisition of optimal bone mass in childhood and adolescence. *Trends Endocrinol Metab* 2001;12:22–28.
30. National Institutes of Health Consensus Development Conference Statement: Osteoporosis Prevention, Diagnosis, and Therapy. *NIH Consens Statement* 2000, March 27–29;17(1):1–36.
31. Matkovic V. Calcium and peak bone mass. *J Intern Med* 1992; 231:151–60.
32. Lai HC, FitzSimmons SC, Allen DB, Kosorok MR, et al. Persistent growth impairment in children with cystic fibrosis following treatment with alternate-day prednisone. *N Engl J Med* 2000;342: 851–59.
33. Institute of Medicine. Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington DC: National Academy Press, 1997.
34. Couper RT, Corey M, Moore DJ, et al. Decline of exocrine pancreatic function in cystic fibrosis patients with pancreatic insufficiency. *Pediatr Res* 1992:32;179–82.
35. Gaskin KJ, Durie PR, Lee L, et al. Colipase and lipase secretion in childhood-onset pancreatic insufficiency: delineation of patients with steatorrhea secondary to relative colipase deficiency. *Gastroenterol* 1984:86;1–7.
36. Kerem E, Corey M, Kerem BS, et al. The relation between genotype and phenotype in cystic fibrosis-analysis of the most common mutation (DF508). *N Engl J Med* 1990:232;1517–22.
37. Kristidis P, Bozon D, Corey M, et al. Genetic determination of exocrine pancreatic function in cystic fibrosis. *Am J Hum Genet* 1992:50;1175–84.
38. Borowitz D, Evidence for the diagnosis of pancreatic sufficiency. *Pediatr Pulmonol* 2000;29:167–8.
39. Caliari S, Benini L, Sembenini C, et al. Medium-chain triglyceride absorption in patients with pancreatic insufficiency. *Scand J Gastroenterol* 1996:31;90–4.
40. Zentler-Munro PL, Fine DR, Batten JC, et al. Effect of cimetidine on enzyme inactivation, bile acid precipitation, and lipid solubilization in pancreatic steatorrhea due to cystic fibrosis. *Gut* 1985:26;892–901.
41. Heijerman HG, Lamers CB, Bakker W. Omeprazole enhances the efficacy of pancreatin (Pancrease) in cystic fibrosis. *Ann Int Med* 1991;114:200–01.
42. Hendeles L, Dorf A, Stecenko A, et al. Treatment failure after substitution of generic pancrelipase capsules. *JAMA* 1990:263; 2459–61.
43. Jeejeebhoy KN, Ahmed S, Kozak G. Determination of faecal fats containing both medium chain and long-chain triglycerides and fatty acids. *Clin Biochem* 1970;3:157–63.
44. Van Dijk-van Aalst K, Van den Driessche M, van der Schoor S, et al. ^{13}C Mixed triglyceride breath test: a noninvasive method to assess lipase activity in children. *J Pediatr Gastroenterol Nutr* 2001:32;579–85.
45. Borowitz D, Grand RJ, Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Pediatr* 1995;127:681–84.
46. FitzSimmons SC, Burkhart GA, Borowitz D, et al. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med 1998:336;1283–1289.
47. Committee on Nutrition, R Kleinman (Ed.), Pediatric Nutrition Handbook, 4th edition, American Academy of Pediatrics, pp. 525, 1998.
48. Center for Disease Control, Recommendations to prevent and control iron deficiency in the United States. MMWR, Apr 3, 1998, 47 (rr-3): 1–36.
49. Lai HC, Corey M, FitzSimmons S, et al. Comparison of growth status in patients with cystic fibrosis between United States and Canada. *Am J Clin Nutr* 1999;69:531–8.
50. Karlberg J, Kjellmer I, Kristiansson B. Linear growth in children with cystic fibrosis: I birth to 8 years of age. *Acta Paeditr Scanda* 1991:80;508–14.
51. Lai H-C, Kasorok MR, Sondel SA, et al. Growth status of children with cystic fibrosis based on the National Cystic Fibrosis Patient Registry: Evaluation of various criteria used to identify malnutrition. *J Pediatr* 1998:132;478–85.
52. Weber AM, Roy CC, Morin CL, et al. Malabsorption of bile acids in children with cystic fibrosis. *N Engl J Med* 1973:289;1001–5.
53. Winklhofer-Roob BM, van't Hof MA, Shmerling DH. Response to oral beta-carotene supplementation in patients with cystic fibrosis: a 16-month follow-up study. *Acta Paediatr* 1995;84: 1132–36.
54. Palin D, Underwood BA, Denning CR. Effect of oral zinc supplementation on plasma levels of vitamin A and retinol-binding protein in cystic fibrosis. *Am J Clin Nutr* 1979;32:1253–59.

55. 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.
56. Winklhofer-Roob BM, van't Hof MA, Shmerling DH. Long-term oral vitamin E supplementation in cystic fibrosis patients: RRR-alpha-tocopherol compared with all-rac-alpha-tocopheryl acetate preparations. *Am J Clin Nutr* 1996;63:722–28.
57. Rashid M, Durie P, Andrew M, et al. Prevalence of vitamin K deficiency in cystic fibrosis. *Am J Clin Nutr* 1999;70:378–82.
58. Lepage G, Champagne J, Ronco N, et al. Supplementation with carotentoids corrects increased lipid peroxidation in children with cystic fibrosis. *Am J Clin Nutr* 1996;64:87–93.
59. Renner S, Rath R, Rust P, et al. Effects of beta-carotene supplementation for six-months on clinical and laboratory parameters in patients with cystic fibrosis. *Thorax* 2001;56:48–52.
60. 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.
61. Lindblad A, Diczfalusy U, Hulcrantz R, et al. Vitamin A Concentration in the liver decreases with age in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1997;24:264–70.
62. Rayner RJ, Tyrell JC, Hiller EJ, et al. Night blindness and conjunctival xerosis caused by vitamin A deficiency in patients with cystic fibrosis. *Arch Dis Child* 1989;64:1151–56.
63. Duggan C, Andrew CA, Agil A, et al. Am J Clin Nutr. Vitamin A status in acute exacerbations of cystic fibrosis. *Am J Clin Nutr* 1996;64:635–39.
64. Hahn TJ, Squires AE, Halstead LR, et al. Reduced serum 25-hydroxyvitamin D concentration and disordered mineral metabolism in patients with cystic fibrosis. *J Pediatr* 1979:94;38–42.
65. Winklhofer-Roob BM, Tuchschmid PE, Molinari L, et al. Response to a single oral dose of all-rac-alpha-tocopheryl acetate in patients with cystic fibrosis and in healthy individuals. *Am J Clin Nutr* 1996;63:717–21.
66. Beker LT, Ahrens RA, Fink RJ, et al. Effect of vitamin K-1 supplementation on vitamin K status in cystic fibrosis patients. *J Pediatr Gastroenterol Nutr* 1997;24:512–17.
67. Wilson DC, Rashid M, Durie PR, et al. Treatment of vitamin K deficiency in cystic fibrosis: effectiveness of a daily fat-soluble vitamin combination. *J Pediatr* 2001;138:851–55.
68. Roigers V, Dab I, Brokaert R, et al. Long-chain nonesterified fatty acid patterns in plasma of cystic fibrosis patients and their parents. *Pediatr Res* 1980;14:1088–91.
69. Christophe AB, Warwick WJ, Holman RT. Serum fatty acid profiles in cystic fibrosis patients and their patrents. *Lipids* 1994;29: 569–75.
70. Roulet M, Frascarolo P, Rappaz I, et al. Essential fatty acid deficiency in well nourished young cystic fibrosis patients. *Eur J Pediatr* 1997:156:952–56.
71. Lloyd-Still JD, Bibus DM, Power CA, et al. Essential fatty acid deficiency and predisposition to lung disease in cystic fibrosis. *Acta Paediatr* 1996;85:1426–32.
72. 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 USA* 1999;96: 13995–14000.
73. Bhudhikanok GS, Lim J, Marcus R, et al. Correlates of osteopenia in patients with cystic fibrosis. *Pediatrics* 1996:9;103–11.
74. Henderson RC, Madsen CD. Bone mineral content and body composition in children and adults with cystic fibrosis. *Pediatr Pulmonol* 1999:27;80–4.
75. Mortensen LA, Chan GM, Alder SC, et al. Bone mineral status in prepubertal children with cystic fibrosis. *J Pediatr* 2000:136; 648–52.
76. Keevil B, Rowlands D, Burton I, et al. Assessment of iron status in cystic fibrosis patients. *Ann Clin Biochem* 2000:37;662–65.
77. Alter JL, Hebst JJ, Landaw SA, et al. Relative anemia and iron deficiency in cystic fibrosis. *Pediatr* 1983:71;810–14.
78. Ehrhardt P, Miller MG, Littlewood JM. Iron deficiency in cystic fibrosis. *Arch Dis Child* 1987:62;185–87.
79. Keevil B, Rowlands D, Burton I, et al. Assessment of iron status in cystic fibrosis patients. *Ann Clin Biochem* 2000:37;662–65.
80. Easley D, Krebs N, Jefferson M, et al, Effect of pancreatic enzymes on zinc absorption in cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1998:26;136–39.
81. Krebs NF, Westcott JE, Arnold TD, et al. Abnormalities of zinc homeostasis in young infants with cystic fibrosis. *Pediatr Res* 2000:48;256–61.
82. Di Sant Agnese PA, Salt depletion in cold weather in infants with cystic fibrosis. *JAMA* 1960:84;2014–21.
83. Laughlin JJ, Brady MS, Eigen H. Changing feeding trends as a cause of electrolyte depletion in infants with cystic fibrosis. Pediatr 1981;68:203–207.
84. Legris GJ, Dearborn D, Stern RC, et al. Sodium space and intravascular volume: Dietary sodium effects in cystic fibrosis and healthy adolescent subjects. *Pediatr* 1998:101;48–568.
85. Stern RC, Canda ER, Doershuk CF. Use of nonmedical treatment by cystic fibrosis patients. *J Adolesc Health* 1992;13:612–15.
86. Marcus M, Lee SK, Lai HC. Use of alternative medicines in children and adults with CF. *Building Block* 2000;24:12–14.
87. Committee on Children with Disabilities, American Academy of Pediatrics, Counseling families who choose complementary and alternative medicine for their child with chronic illness or disability. *Pediatrics* 2001:107;598–601.
88. Malfroot A, Dab I. New insights on gastro-oesophageal reflux in cystic fibrosis by longitudinal follow-up. *Arch Dis Child* 1991: 66;1339–45.
89. Scott RB, O'Laughlin EV, Gall DG. Gastroesophageal reflux in patients with cystic fibrosis. *J Pediatr* 1985;106:223–27.
90. Rudolph CD et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children. Recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 2001:32;suppl 2 S1–S31.
91. Moran A, Doherty L, Wang X, et al. Abnormal glucose metabolism in cystic fibrosis. *J Pediatr* 1988;133:10–17.
92. Moran A, Hardin D, Rodman D, et al. Diagnosis, Screening and management of cystic fibrosis related diabetes mellitus: A consensus report. *Diabet Res and Clin Pract* 1999;45:61–73.
93. Sokol RJ, Durie PR. Recommendations for management of liver and biliary tract disease in cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1999;28 Suppl 1:S1–13.
94. Lai HC, Kosorok MR, Laxova A, et al. Nutritional status of patients with cystic fibrosis with meconium ileus: a comparison with patients without meconium ileus diagnosed early through neonatal screening. *Pediatrics* 2000;105:53–61.
95. Crist W, McDonnell P, Beck M, et al. Behavior at mealtimes in the young child with cystic fibrosis. *J Devel Behav Pediatr* 1994; 15:157–61.
96. Stark LJ, Jelalian E, Powers SW, et al. Parent and child mealtime behavior in families of children with cystic fibrosis. *J Pediatr* 2000:136;195–200.
97. Hanning RM, Blimkie C, Bar-Or O et al, Relationships among nutritional status and skeletal respiratory muscle function in cystic fibrosis: does early dietary supplementation make a difference. *Am J Clin Nutr* 1993;57:580–k.
98. Parsons HG, Beaudry P, Dumas A, et al. Energy needs and growth in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1983;2:44–9.
99. Kalnins D, Durie PR, Corey M, et al. Are oral dietary supplements effective in the nutritional management of adolescents and adults with CF. *Pediatr Pulmonol* 1996;Suppl 11:314–5.
100. Rettammel AL, Marcus M, Farrell PM, et al. Oral supplementation with a high-fat, high-energy product improves nutritional status and alters serum lipids in patients with cystic fibrosis. *J Am Diet Assoc* 1995;95:454–9.

101. Erskine JM, Lingard CD, Sontag MK, et al. Enteral nutrition for patients with cystic fibrosis: comparison of a semi-elemental and non-elemental formula. *J Pediatr* 1998;132:265–9.
102. Durie PD, Newth C, Forstner G, et al. Malabsorption of medium-chain triglycerides in infants with cystic fibrosis: correction with pancreatic enzyme supplements. *J Pediatr* 1980:862–4.
103. Kane RE, Hobbs PJ, Black PG. Comparison of low, medium and high carbohydrate formulas for nighttime enteral feedings in cystic fibrosis patients. *J Parent Ent Nutr* 1990;14:47–52.
104. Hardin DS, LeBlanc A, Lukenbaugh S, et al. Proteolysis associated with insulin resistance in cystic fibrosis. *Pediatr* 1998;101: 433–37.
105. Lanng S, Thorsteinsson B, Nerup J, et al. Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. *Acta Paediatr* 1994;83:849–53.
106. Hardin DS, Ellis KJ, Dyson M, et al. Growth hormone improves clinical status in pre-pubertal children with cystic fibrosis: results of a randomized controlled trial. *J Pediatr* 2001; 139:636–42.
107. Hardin DS, Ellis KJ, Dyson M, et al. Growth hormone decreases protein catabolism in children with cystic fibrosis. *J Clin Endocrinol Metab* 2001;86;4424–28.
108. Marchand V, Baker SS, Stard TJ, et al. Randomized, double-blind, placebo-controlled pilot trial of megestrol acetate in malnourished children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2000;31:264–69.
109. Newkirk M, Martinez JC, Ewig J, et al. Adrenal suppression in children with cystic fibrosis treated with megestrol acetate (Megace). *Pediatr Pulmonol* 2001;Suppl 20;323.
110. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Food and Nutrition Board, Institute of Medicine, National Academy Press, Washington, DC, 2001.