JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eCysticFibrosis Review

Presented by
The Johns Hopkins University School of Medicine, The Institute of Johns Hopkins Nursing and the Postgraduate Institute for Medicine

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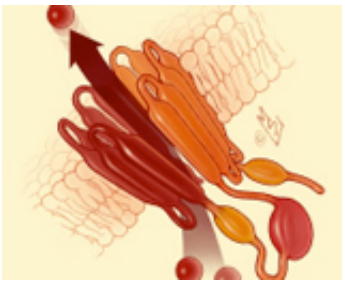

MARCH 2009: VOLUME 1, NUMBER 6

Optimizing Nutritional Status in Cystic Fibrosis

In this Issue...

The great majority of patients with cystic fibrosis (CF) are pancreatic insufficient, with nutrition being a recognized component of care since the 1970s. It was at about this time that the current approach to nutritional care (ie, a large amount of food and a high-fat intake, with enzyme replacement to optimize absorption) became widely accepted. In the following decade, the pancreatic enzyme products were greatly improved, with most now withstanding gastric protein degradation and arriving in the duodenum with the ability to aid in food digestion and absorption. CF nutritional care supports both improved medical outcomes and patient quality of life. This issue of the eCF Review will highlight important changes in our understanding of CF nutrition and the resulting impact on clinical care.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Discuss the role of nutritional care and growth monitoring in children and adults with cystic fibrosis (CF) and pancreatic insufficiency (PI)
- Identify the key body mass index–related recommendations from the 2008 Practice Recommendations for Nutrition-Related Management
- Summarize new data on the determination of pancreatic status, on the efficacy of behavioral intervention for growth failure in young children, and on the need for evaluating outcomes associated with the use of fat-soluble vitamin supplementation in children with CF and pancreatic insufficiency

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THIS ISSUE

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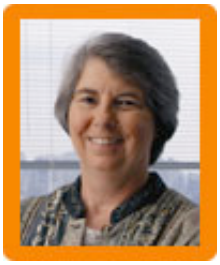

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COMMENTARY

After some debate, the nutritional care of patients with CF and pancreatic insufficiency is now considered an essential component of treatment, along with antibiotics and other pulmonary medications. Epidemiologic studies have demonstrated that improved growth and nutritional status in infants and children with CF are associated with a slower decline in pulmonary function. Nutritional interventions resulting in changes in lung disease further support the importance of optimal growth and nutritional status in the care of patients with CF. The assessment of nutritional status is required at each CF Center when evaluating adults, which also involves the assessment of growth and development in children. As reviewed herein, the recent report by Zhang and Lai provided evidence that care teams should use the body mass index (BMI) approach (ie, BMI percentiles [BMIp] in children and BMI values in adults) to assess weight-for-height status and to screen for malnutrition, and should discontinue the use of percentage of ideal body weight (%IBW). This change will reduce the methodologic difficulties involved in assessing patients who are shorter or taller than average. The 2008 Evidence-Based Practice Recommendations for Nutrition-Related Management (summarized by Stallings and colleagues in this review) also support discontinuing the use of %IBW in individuals with CF. With the availability of the 2006 World Health Organization (WHO) Growth Charts, the CF community now has excellent BMI data for use in patients from birth to 5 years of age, thus allowing BMI assessment to occur in the youngest patients. We advocate switching from the 2000 Centers for Disease Control and Prevention (CDC) Growth Charts to the WHO Growth Charts in patients from birth to 5 years of age. Focusing on younger children, the article by Powers and associates reviewed in this newsletter demonstrated that behavioral and nutritional treatment improves food intake and growth in toddlers and preschoolers with CF. This complements the previous studies and body of work by Stark, Powers and coworkers conducted in older children demonstrating to participants in the patients' "food and snack" activity circle that combining nutrition and behavioral guidance is effective in treating growth failure. Birth cohort data from the Cystic Fibrosis Foundation (CFF) Patient Registry continue to reveal that patients fail to completely "catch up" in weight and length/height following a diagnosis of CF. The birth cohort group data demonstrate that the peak attainment is still at less than the 50th percentile and that group growth data are best for children around 4 to 5 years of age, then begin to decline. We can do better than this. This assertion emanates from multiple studies reporting that improved growth in young children translates into improved lung status at school age (when lung function testing begins) and as children get older.

The article by Borowitz and associates is presented as the lead-in for a discussion on the misdiagnosis of pancreatic status. This is a more common occurrence than previously believed, with data suggesting that such misdiagnosis may be occur as often as 10% of the time or more. This means that some patients are receiving enzyme replacement therapy that is not needed. The safety profile of enzymes is excellent and serious adverse events are very rare. However, there are financial costs and burdens associated with prescribing and taking unneeded medications. Fewer patients are misdiagnosed as having pancreatic sufficiency who actually have pancreatic insufficiency, with the delay in receiving appropriate medication having a negative impact on these individuals. The monoclonal fecal elastase-1 assay is available and affordable. The CF community will be discussing whether this assay should be a standard of care for all or possibly for those patients who are not delta F 508 homozygous, in whom a pancreatic insufficient status is almost universal. Another nutritional care topic covered in this review is the impact of vitamin and mineral supplements designed and marketed for the care of patients with CF. The report by Graham-Maar and colleagues discussed in this review shows that in the current CF care setting (with attention to nutritional management, improved adherence, and the use of high-dose, fat-soluble vitamin products), we need to monitor patients for the possibility of excess fat-soluble vitamin intake and elevated blood concentrations, in addition to the traditional surveillance for suboptimal and deficient levels.

Nutritional research will continue to provide evidence to help guide the management of patients with CF. Now that people are living longer and better CF care is available across the life span, new nutrition-related successes and areas of concern will be reported.

DISCONTINUED USE OF PERCENTAGE OF IDEAL BODY WEIGHT AS A MEASUREMENT OF NUTRITIONAL STATUS IN CHILDREN WITH CYSTIC FIBROSIS

Zhang Z, Lai HJ. **Comparison of the use of body mass index percentiles and percentage of ideal body weight to screen for malnutrition in children with cystic fibrosis.** *Am J Clin Nutr.* 2004;80(4):982-991.

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Nutritional status measurements of weight-for-height and height-for-age and gender are used to calculate such indicators as ideal body weight (IBW) and body mass index (BMI), in order to determine the adequacy of weight-for-stature and fat stores in patients with CF. These criteria are then compared with reference values to track growth and tissue accretion, and are associated with clinical outcomes in CF. Zhang and Lai assessed the agreement of these indicators across a range of stature-for-age and the relationship of these criteria to pulmonary status (forced expiratory volume in 1 second; FEV_1). Data from the 2000 CFF Patient Registry were used and provided 13,021 observations in children 2 to 20 years of age. Malnutrition was defined as %IBW <90% or BMIp <15th percentile. FEV_1 was available for subjects >6 years of age. In individuals of average stature (ie, height-for-age between the 25th and 75th percentiles), %IBW and BMIp were in general agreement. Discordance was observed in patients of short stature (<25th percentile), with %IBW higher than corresponding BMIp values. With respect to height-for-age >75th percentile, more children were classified as malnourished by %IBW than by BMIp. Discordance increased as age increased (>12 years) and was significantly ($P<0.0001$) greater in females. The consequences of discrepancies between the 2 indicators significantly changed the prevalence of malnutrition in children who were either shorter or taller than subjects of average height. These data showed that compared with BMIp, the %IBW approach underestimated malnutrition in shorter subjects and overestimated malnutrition in taller subjects, and these differences were more pronounced in adolescent and females patients. A limitation of this study was that a more direct measurement of body composition, such as fat stores, was not available for comparison. A second important contribution of this investigation was determining the association of each nutritional indicator to FEV_1. Compared with %IBW, BMIp was shown to have a stronger association with FEV_1 in children with CF. Therefore, BMI percentiles were a more clinically informative indicator of nutritional status as compared to %IBW.

In a study by Lai and Shoff,[1] BMIp criteria (BMI <15th percentile) were compared with nutritional status in subjects with CF classified by %IBW. The analysis resulted in a 6% reduction (from 33% to 27%) in nutritional failure rate in a sample of 14,702 subjects across 113 US CF Centers.[1] The relationship between BMI and pulmonary function was also evaluated in the 2005 CFF Patient Registry. Based on the findings, BMIp, rather than %IBW, was incorporated into the 2008 nutrition recommendations (reviewed by Stallings and associates in this newsletter), with the clinical goal being to maintain a pattern of growth resulting in a BMIp >50th percentile in children. When BMIp >50th percentile was applied to FEV_1 in the aforementioned study by Lai and Shoff,[1] the authors found that 57% of the patients with CF between 2 and 20 years of age had values below this leading nutritional status goal.

The 2000 CDC Growth Charts[2] do not contain BMI data for children from birth to 2 years of age. The 2006 WHO Growth Charts[3] include BMIp and z-scores for children from birth to 5 years of age. Additional studies are needed to evaluate these relationships in infants and toddlers with CF.

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1. Lai HJ, Shoff SM. Classification of malnutrition in cystic fibrosis: implications for evaluating and benchmarking clinical practice performance. *Am J Clin Nutr.* 2008; 88(1):161-166.
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3. World Health Organization. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva, Switzerland: WHO Press; 2006.

NEW EVIDENCE-BASED PRACTICE RECOMMENDATIONS ON THE NUTRITIONAL MANAGEMENT OF PATIENTS WITH CYSTIC FIBROSIS

Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H; Clinical Practice Guidelines on Growth and Nutrition Subcommittee; Ad Hoc Working Group. **Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systemic review.** *J Am Diet Assoc.* 2008;108(5):832-839.

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Consensus committee reports have previously provided recommendations on the nutritional management of patients with CF. The 2007 CFF Subcommittee on Growth and Nutrition was charged with the responsibility of providing evidence-based practice recommendations for energy intake, nutritional and growth goals, and guidelines on generic and non-generic brands and dosages of pancreatic enzyme replacement therapy (PERT) in children and adults with CF and pancreatic insufficiency. The report summarized the systemic review of the literature in the selected areas. A total of 57 publications from the 1008 reviewed were included from the 1988 to 2005 time frame for multiple databases. Key clinical care findings included the following:

- Good evidence that increased energy intake resulted in improved weight gain
- Behavioral interventions to increase nutritional intake, in conjunction with nutritional counseling, were effective in children 1 to 12 years of age, as part of the overall management of growth deficits
- Improved growth parameters (ie, weight-for-age, height-for-age, weight-for-height percentiles) were associated with better pulmonary outcomes (ie, FEV_1) and increased survival among children and adults
- Since the data were insufficient to offer recommendations regarding the efficacy of generic PERT therapy, the use of generic PERT was not recommended. In addition, the data were insufficient to make changes to the existing PERT dosage recommendation

The energy intake recommendations were made for adults and children >2 years of age, and were broadly described as being between 110% and 200% of energy needs of the healthy population of a similar age and gender. A study published after this review suggested that from birth to 2 years of age, an energy intake of >120% of the estimated energy optimizes long-term growth outcomes.[3]

A second contribution of the CFF Subcommittee was to conduct new analyses, and to report the findings on growth and nutritional monitoring from the 2005 CFF Patient Registry. These data were based on 22,700 subjects from 117 US CF Centers. A BMIp

approach was used rather than %IBW, based on the work by Lai and Zhang reviewed earlier in this newsletter. Key clinical care findings and recommendations included the following:

- Improved BMIp in children correlated with improved FEV_1, with cohorts of younger children having a better status than older cohorts and males having a better FEV_1 than females
- Subjects with better growth patterns at 2 years of age had better FEV_1 values when assessed between 6 and 15 years of age
- In children, achieving and maintaining a BMI >50th percentile for age and gender was recommended, based on the associations with clinical outcomes. Of note, about 54% of the children had a BMI below the recommended 50th percentile for age in the 2005 data set
- Similar gender associations were also seen with BMI and FEV_1 in adults with CF; pancreatic insufficiency and gender differences were also observed in adult subjects
- Achieving and maintaining a BMI >22 in women and >23 in men was recommended, based on the association with improved pulmonary outcomes. Of note, only 32% of women and 35% of men met the BMI recommendation in the 2005 data set. The sample of adult subjects with BMI >29 was small and insufficient for analyses of the association between BMIp and FEV_1 to be conducted.

These findings emphasize that early, successful nutritional management is key to long-term nutritional and growth status, and contributes to pulmonary health in patients with CF and pancreatic insufficiency.

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BEHAVIORAL AND NUTRITIONAL INTERVENTIONS IN CHILDREN WITH CYSTIC FIBROSIS

Powers SW, Jones JS, Ferguson KS, Piazza-Waggoner C, Daines C, Acton JD. **Randomized clinical trial of behavioral and nutrition treatment to improve energy intake and growth in toddlers and preschoolers with cystic fibrosis.** *Pediatrics.* 2005;116(6): 1442-1450.

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Behavioral interventions combined with nutritional counseling and supplementation have been used to increase caloric intake in individuals with CF. As previously reviewed herein by Stallings and coworkers, the 2008 CF Nutrition Recommendations support the efficacy of this approach in children. The current study was published after the period of the literature review that was included in the 2008 CF Nutrition Recommendations. This study by Powers and colleagues contributes information on the efficacy of a combined behavioral/ nutritional approach for increasing caloric intake and growth in patients with CF.

This was a prospective, randomized, usual-care, controlled trial conducted in a small group of children (1.5 to 4 years of age) with CF and pancreatic insufficiency. The usual-care group received standard CF Center–based care. The children in the behavioral intervention arm received individualized nutritional counseling sessions that targeted increased energy intake in one type of meal per week, with a stepwise increase over the 8-week intervention period to affect an increase in calories for all meals and snacks. The treatment curriculum focused on 3 goals:

- Increasing calorie and fat intake, with the goal being to meet the 120% to 150% recommended dietary allowance (RDA) for energy and 35% to 40% calories derived from fat
- Ensuring appropriate dosage and timing of PERT plus regular meal schedule
- Teaching effective parental management skills, in order to address behavioral challenges encountered in toddlers and preschoolers at mealtime

The intervention group had an average caloric intake increase of 842 kcal/day, compared with a decrease of 131 kcal/day in the control group. Prior to the intervention, none of the children in the behavioral intervention group met the >120% RDA for energy and 35% to 40% fat goals; all children achieved these goals posttreatment. In comparison, none of the subjects in the control group met either criteria at baseline, and only 1 subject met the energy goal in the posttreatment evaluation. In addition, at the end of the posttreatment assessment, control subjects were invited and chose to undergo the behavioral and nutritional counseling intervention, with replication of the intervention results.

The follow-up evaluation at 3 and 12 months posttreatment demonstrated a sustained increase in energy intake compared with the 8-week assessment, with 89% of subjects maintaining an energy intake >120% of the RDA (approximately 673 kcal/day above baseline). Similar findings were reported at the 12-month posttreatment assessment (approximately 750 kcal/day above baseline). Weight and height velocity for the subjects in the intervention group was at or above the patterns of linear growth observed in healthy children of similar age and gender. Although the sample size was small, these findings suggest that behavioral and nutritional intervention is effective in improving caloric intake, and that the effects are durable and sustainable. This study adds to the previous literature supporting this approach for the treatment of undernutrition in children with CF. These data emphasize the need for multidisciplinary care and skills among members of the CF team.

USE OF FECAL ELASTASE-1 FOR VERIFICATION OF PANCREATIC STATUS

Borowitz D, Baker SS, Duffy L, et al. **Use of fecal elastase-1 to classify pancreatic status in patients with cystic fibrosis.** *J Pediatr.* 2004;145(3):322-326.

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Pancreatic status, the major determinant of fat and nutrient malabsorption in patients with CF, has implications for long-term clinical outcomes. Direct pancreatic assessment by duodenal fluid aspiration following secretin and cholecystokinin stimulation is a sensitive and specific test that is expensive, invasive, and not widely used in research or clinical care. Indirect testing with 72-hour fecal collection from an adequate fat diet, used to calculate the coefficient of fat absorption, is the standard test. In recent years, pancreatic elastase antibodies have been identified and used to develop a new approach to pancreatic testing. Elastase is not degraded during passage through the digestive tract and is detected in human stool samples. Fecal elastase-1 (FE-1) can be assessed by either monoclonal or polyclonal commercial assays, which has been the source of some difficulty in the care of patients with CF. The monoclonal assay has greater specificity for

human pancreatic elastase and the polyclonal assay reacts to different elastase antigens, including porcine. Since the monoclonal assay does not react to porcine elastase, it can be used in patients with CF who are taking porcine-derived PERT while under evaluation.[1,2]

Borowitz and associates utilized monoclonal FE-1 to determine the pancreatic status of subjects with CF, comparing this with the clinical pancreatic status and use of PERT in 1215 children and adult subjects from 33 US CF Centers. Monoclonal FE-1 testing was performed, and the value of >200 µg/g stool was used to define pancreatic sufficiency. Mean FE-1 was approximately 61 µg/g stool (median 0, range 0 to 867), and 88% of the subjects had FE-1 levels <200 µg/g. The results of the study indicated that 2% of these subjects were misclassified as being pancreatic sufficient when they were actually pancreatic insufficient and were not receiving PERT. Approximately 12% of the subjects had fecal elastase levels >200 µg/g stool, with about 40% of them being correctly treated (ie, not taking enzymes) and about 60% being inappropriately prescribed PERT. A total of 18 subjects had FE-1 levels between 100 and 200 µg/g, representing an area of diagnostic uncertainty.

A smaller study by Cohen and coworkers[3] using FE-1 <15 µg/g stool also demonstrated that about 12% of the subjects clinically assessed as being pancreatic insufficient had been misclassified. A number of studies have proposed an FE-1 cutoff, with levels of 15, 100, and 200 µg/g stool suggested.[3-5] Although there is no CF standard for defining pancreatic insufficiency/pancreatic sufficiency, current consensus is that FE-1 <15 µg/g signifies pancreatic insufficiency and FE-1 >200 µg/g signifies pancreatic sufficiency. In summary, the FE-1 monoclonal assay is a useful objective test for determining pancreatic status (pancreatic insufficiency vs pancreatic sufficiency), with an accurate diagnosis essential for optimal clinical care.

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VITAMIN A STATUS IN PATIENTS WITH CYSTIC FIBROSIS: NEED FOR BALANCE

Graham-Maar RC, Schall JI, Stettler N, Zemel BS, Stallings VA. **Elevated vitamin A intake and serum retinol in preadolescent children with cystic fibrosis.** *Am J Clin Nutr.* 2006;84(1):174-182.

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Graham-Maar and colleagues presented data on food and supplement-derived vitamin A intake, and resulting serum retinol concentrations, in 73 preadolescent (8 to 11 years of age) children with CF, pancreatic insufficiency, and mild lung disease from 13 US CF

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Centers. Vitamin A deficiency is a known consequence of CF and pancreatic insufficiency, particularly in infants and children with delayed diagnosis, and in those who do not regularly take high-dose, preformed vitamin A (retinol) supplements. Beta-carotene, a water-soluble compound, converts to vitamin A but at a much lower ratio than previously thought. Guidelines for vitamin A intake (all sources) are now expressed as retinol activity equivalents (RAEs), with this change allowing for improved understanding of optimal total intake (preformed, pro-vitamin A, carotenoids); risk for deficiency; and excessive intake. Vitamin A food intake in the CF cohort was about 165% of the RDA, which was similar to that in healthy US children. As expected, supplement intake was high and, when combined with dietary intake, resulted in a mean total vitamin A intake in 78% of the children with CF that was above the tolerable upper limit set for healthy children. The CF vitamin A intake requirement is higher than that in healthy individuals, with >20% of children with CF in this study exceeding this CF-specific intake. The mean serum retinol concentration was unexpectedly high (52 ±13 µg/dL) and was significantly ($P<0.001$) higher than that in a national sample of healthy children (37 ± 10 µg/dL). In a second study from this group, Maqbool and associates[1] repeated their evaluation of patients with CF and pancreatic insufficiency in a broader age range (8 to 25 years). The authors confirmed high food and supplemental vitamin A intake, reporting a median serum retinol concentration of 80 µg/dL, with 58% of the patients above the reference range (30 to 72 µg/dL) in the healthy US population of similar ages.

Vitamin A is a fat-soluble vitamin that has a well-described toxicity profile and is stored in liver stellate cells. Hepatic collagen is produced (fibrosis) by the stellate cells via liver injury, including the hepatic damage of CF-associated liver disease. Little is known about hepatic vitamin A stores in contemporary, relatively healthy people with CF. Most liver measurements are from autopsy or from liver biopsy indicated by clinical liver disease.[2,3] Concern exists that high vitamin A intake and high serum retinol concentrations may result in toxicity. Serum retinol is an excellent measure of vitamin A status in the “deficient to normal” range, but it is not a good indicator of toxicity. This concern over toxicity is balanced by the necessity for vitamin A supplementation associated with chronic fat-soluble vitamin malabsorption. In addition, vitamin A is an antioxidant compound that may improve health in the setting of CF and chronic inflammation. Fahed and colleagues[4] showed a positive association between improved retinol concentration and better FEV_1 in patients with CF across the full range of FEV_1 values, and in both pancreatic insufficient and pancreatic sufficient patients. Ongoing monitoring of vitamin A status (serum retinol) is necessary to ensure that the supplementation is providing sufficient intake and adequate status. In patients with high retinol concentrations, the CF care team may consider reducing the supplemental vitamin A intake and then rechecking the serum level, with the aim being to achieve normal, but not high, values. Additional research is needed to determine optimal doses of vitamin A and a method to screen for high liver stores, which may represent toxicity and an avoidable risk for liver damage.

References

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