Cystic fibrosis is an autosomal recessive disease associated with progressive pulmonary disease and exocrine pancreatic insufficiency. The effect of malnutrition leads directly to a decline in pulmonary function and fat malabsorption due to pancreatic insufficiency. As a result, patients should be screened for malnutrition during clinic visits. Several treatment modalities for malnutrition exist, but the cornerstone of therapy includes dietary management and pancreatic enzyme replacement therapy. Pancreatic enzyme replacement therapy should be dosed at less than 10,000 U/kg/day to prevent medication-related complications. All cystic fibrosis patients should be screened for malnutrition as well as other gastrointestinal disorders.
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transport through the CFTR (2). Certain CFTR genotype mutations are more frequently associated with PI, although there is less known correlation of these mutations with other cystic fibrosis-associated gastrointestinal diseases, especially in older patients (4,5). Recently, SERPINA1 polymorphisms (the gene for alpha 1-antitrypsin) have been identified as contributing to the development of CF-related liver disease (6).

Chorionic villous sampling and the newer technique of fetal DNA detection in maternal plasma through digital relative mutation dosage selection has the potential for prenatal diagnosis as well as early identification of significant CF genotypes (7).

There are many ways to diagnose PI, including the “gold standard” of a 72-hour fecal fat balance study; however, the recent development of measuring fecal elastase by enzyme-linked immunosorbent assay has proven to be an efficient way to diagnose PI (8). Measurement of fecal elastase is accurate, noninvasive, and requires minimal sample volume (9).

NUTRITION AND CYSTIC FIBROSIS

Multiple studies suggest that good nutritional status improves lung function in CF patients. One of the first studies to demonstrate that good nutrition was associated with improved lung function in CF occurred in Australia in which a link was noted between the decline in forced vital capacity (FVC) and body cell mass, calculated from a derivative of total body potassium (10). Another large prospective study from the University of Minnesota demonstrated the importance of weight with regard to lung function in CF patients. This study showed that higher baseline weight as well as greater weight gain over a 2-year follow-up period was associated with a higher predicted forced expiratory volume in the first second (FEV₁) in CF patients (11). McPhail et al compared pediatric CF patients from 1985 and 1992 as well as 1993 to 2000 at a single CF center and found a higher FEV₁, slower rate of pulmonary decline (percent decline in FEV₁ per year), as well as a higher body mass index (BMI) in the group from 1993 to 2000. These changes were related to a higher baseline BMI, absence of Pseudomonas aeruginosa infection, and use of dornase alfa therapy (Pulmozyme™, Genetech, San Francisco, California). This study was one of the first to show a direct relationship between nutrition and lung function in pediatric patients. The most likely etiology for improvement was multi-factorial including pancreatic enzyme replacement therapy (PERT), use of gastrostomy tubes for feeds, and improved nutrition counseling (12).

It appears that female CF patients with PI undergoing puberty have an increased resting energy expenditure, suggesting that this specific population requires special nutritional attention (13). Other studies have demonstrated that female gender (regardless of age) and low patient weight after the age of 9 years (regardless of gender) are risk factors for FEV₁ decline in CF patients (14). The rapid decline in lung function in relation to nutrition continues throughout the first 2 decades of life, as CF patients with malnutrition have been observed to have up to a 20% decrease of FEV₁. This decline especially is noted if such patients have an associated P. aeruginosa infection (15). Nutritional status also is important in healthier CF patients as those patients with mild lung disease will have less FEV₁ decline if they have a good z score for weight, suggesting appropriate nutrition management should be implemented early in each patient’s life (16).
NUTRITION THERAPIES IN CYSTIC FIBROSIS

The cornerstone of nutrition management is careful measurement of anthropometrics (including height and weight), evaluation of lung function, and evaluation for PI. CF patients should be counseled to have a caloric intake of 120–150% of energy requirements for age and gender (17–19). Unfortunately, many pediatric CF patients do not follow this recommended dietary amount and do not receive enough of their total calories from fat, as it is recommended that 40% of their diet should consist of fat intake (20). A high-fat diet should not lead to an increased respiratory carbon dioxide, especially when combined with a low carbohydrate diet (21). Dieticians with CF patient experience are imperative in the management of these nutritional issues (22).

Supplementation with tube feedings should be considered as an early treatment modality in any CF patient who is showing signs of growth impairment, and gastrostomy tube placement for use in nocturnal tube feeds is recommended in this setting after evaluation for other co-morbidities such as pulmonary exacerbation and CFRD (23). Formula type, either elemental or non-elemental, is not an issue as long as PERT is utilized (23,24).

Appetite stimulants are of potential benefit only in the short term to increase appetite, maintain nutrition, and prevent FEV₁ decline. Both cyproheptadine hydrochloride (a histamine and serotonin antagonist) and megestrol acetate (a progesterone derivative) are effective in increasing weight in pediatric CF patients, but they are only effective in those patients with early satiety (25). Megestrol acetate can lead to adrenal suppression, and this side effect should be considered when this medication is used (26).

Other medical modalities have been studied as potential weight-gain therapies. Specifically, human growth hormone has been studied in children with CF to assess its growth effect. Although height, weight, lean tissue mass, and bone mineral content (measured by Dual Energy X-ray absorptiometry) improved in patients treated with growth hormone, no significant change in predicted pulmonary function was noted between those patients receiving growth hormone for one year versus those receiving growth hormone for 2 years (27). Growth hormone may be an appropriate therapeutic option, but it may not necessarily have the same clinical effect as adequate nutrition and is expensive. More studies are needed to evaluate this treatment modality (28).

UPDATE ON PERT

The initial evaluation of all CF patients should include assessment for PI as well as a prescribed PERT as the cornerstone of medical therapy to prevent malnutrition. Fat-soluble vitamin supplementation will be necessary in PI, and these vitamins should be used in all patients requiring PERT (2). PERT dosing should not exceed 10,000 units of lipase per kilogram per day (U/kg/day) to prevent fibrosing colonopathy which leads to colonic obstruction necessitating surgical resection. Patients at risk of fibrosing colonopathy may present with bloody diarrhea prior to obstruction, and a barium enema may show a narrowed colonic lumen (29). The incidence of fibrosing colonopathy has declined dramatically since the publication of guidelines determining safe PERT levels (30).

The symptoms of PI (poor growth, steatorrhea, fat-soluble vitamin malabsorption) typically occur when lipase production is less than 10% of normal levels. PERT attempts to simulate actual pancreatic enzyme release. In pancreatic sufficiency, pancreatic enzymes increase up to 6 times basal levels within 60 minutes in the post-prandial setting before decreasing back to baseline levels within 4 hours. Regardless of how compliant a patient adheres to a medical regimen, PERT always will have clinical variability compared to in vivo pancreatic enzyme production due to gastric acid proteolysis of supplemented enzymes (31). Therefore, potential clinical symptoms of malabsorption such as abdominal pain, diarrhea, and steatorrhea should not be used solely as an indicator of PERT effectiveness (31,32).

PERT should be given just before or during a meal with a recommended initial dose of 500 units per kilogram per meal (U/kg/meal) and 250 units per kilogram per snack (U/kg/snack). If a patient cannot swallow a whole capsule, the capsule may be opened and the contents mixed with a small amount of appropriate food, such as applesauce. Chewing a PERT capsule should be discouraged. Once a patient and the patient’s family are comfortable with PERT, dosing is increased gradually.
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Figure 2. A 15-year-old male presented with abdominal pain and worsening flatulence by history. An abdominal flat plate revealed DIOS that responded well to high-dose osmotic laxative therapy.

until symptoms of steatorrhea improve or until a maximum dose is reached of 2500 U/kg/meal or 10,000 U/kg/day (33). In the past, the actual dosing of units of lipase per capsule could be higher than what was stated on the package insert. The reason for this difference was that the enzymes degraded over time. Therefore, manufacturers would overfill PERT capsules to ensure that actual enzyme content was in with the allowed legal range of the labeled enzyme dose until the product expiration date (34).

Enteric-coated minicapsule PERT preparations can protect against gastric acidity and proteolysis in contrast to non-enteric coated preparations (34). Concomitant acid suppression (including H₂-antagonists and proton pump inhibitors) increases gastric and proximal small bowel pH, improves micelle formation, and prevents bile acid precipitation in CF patients (35). It also can improve steatorrhea in patients on high-dose PERT (36). However, the use of bicarbonate buffering in capsule preparations minimizes the need for acid suppression and diminishes PERT degradation (37,38).

In 2006, the United States Food and Drug Administration (FDA) required pharmaceutical companies that manufactured PERTs to submit new drug applications (NDA) for these therapies. NDA require sponsors to conduct clinical trials to demonstrate a relationship between the use and the clinical benefit of PERT. The FDA recommended that such studies should include pediatric patients, and quantification of clinical benefit, including use of the 72-hour fecal fat excretion test, should be evaluated. Such studies are recommended to be parallel, randomized controlled, or crossover in design (34). These FDA recommendations are based on previous research which demonstrated that most marketed PERT had more amylase, lipase, and protease than was claimed on the bottle label. However, some samples had a large decrease in lipase activity after dissolution in simulated stomach acid suggesting that significant PERT preparation variation existed between brands. In the past, the lack of clinical improvement after PERT in some patients may have been due to poor standardization of this drug class which now is being corrected by updating the FDA rulings (34,38).

Other confounders exist in establishing PERT effectiveness, and these factors should be considered when evaluating the CF patient. Such factors include small intestine bacterial overgrowth, impaired pancreatic enzyme secretion, and abnormal hydration of intestinal mucus leading to enterocyte injury and malabsorption. Also, DIOS may develop due to obstruction from food product malabsorption which can lead to significant constipation. Patients with DIOS may complain of “feeling gassy” which can be misconstrued as steatorrhea (Figure 2) (32). DIOS should be treated with osmotic laxative therapy rather than by increasing the PERT dose. Finally, poor growth in CF patients may be due to CFRD. CFRD requires an oral glucose tolerance test for diagnosis as hemoglobin A₁C levels do not correlate with an impaired glucose tolerance in CF patients (39). Although young children with CFRD can be asymptomatic, older children and adults often will present with impaired growth parameters, including height-for-age, weight-for-age, and body mass index, as well as impaired lung function (39,40).

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SUMMARY
The Cystic Fibrosis Foundation has published guidelines for all CF care centers in the United States. Each center should provide multi-discipline counseling and therapy including pulmonary care, gastrointestinal care, as well as genetic and psychosocial counseling. A dietician should be part of the CF care center team, and all centers should have consultative access to a gastroenterologist to assess nutrition as well as to screen and treat CF-associated gastrointestinal disease. An additional recommendation is that either a board-certified pulmonologist or gastroenterologist be a CF care center director (41). Due to the large number of gastrointestinal disorders associated with CF, including malnutrition, it is imperative for a gastroenterologist (either adult or pediatric) to be involved with a CF care center either as part of the care team or as a consultant (42). Screening for CF gastrointestinal complications should be considered an integral part of patient evaluation at scheduled CF care center visits (Table 1). Finally, a good transition plan for nutrition and pulmonary status should exist for all CF patients as they grow older and transfer from a pediatric to an adult care center.

Table 1. Gastrointestinal Complications of Cystic Fibrosis (2,14,24,30)

- Pancreatic insufficiency (more commonly exocrine, but also endocrine)
- Pancreatitis
- Cholelithiasis
- Common bile duct stenosis
- Liver disease (neonatal cholestasis, non-alcoholic fatty liver disease, fibrosis, cirrhosis)
- Distal intestinal obstructive syndrome (DIOS)
- Fibrosing colonopathy
- Clostridium difficile enterocolitis
- Small intestinal bacterial overgrowth
- Gastroesophageal reflux disease
- Gastrointestinal cancer (in adult CF patients)

Author Disclosure
The author’s institution received education funding through Eurand Pharmaceuticals, Inc. (Yardley, PA) to produce this review article.

References