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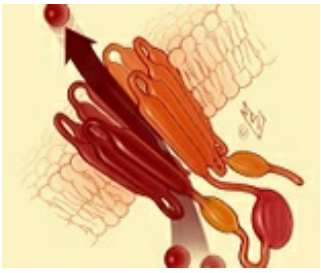

Nutritional Issues in Cystic Fibrosis

In this Issue...

While the use of pancreatic enzymes is a key treatment in cystic fibrosis, evidence-based dosing guidelines and reliable markers of treatment are not available. In addition, it is not clear how new potentiators of CFTR function will affect the long-term need for pancreatic enzyme replacement therapy.

In this issue, Dr. Deepak Agrawal from the University Texas Southwestern Medical Center and Dr. Sarah Jane Schwarzenberg from the University of Minnesota Masonic Children's Hospital review recent evidence describing the positive impact of ivacaftor on growth in cystic fibrosis, the difficulties in determining an appropriate upper limit of PERT dosing for infants with cystic fibrosis, and some of the key factors that affect adherence to enzyme therapy in cystic fibrosis.

LEARNING OBJECTIVES

- Summarize the impact of disease modifying therapies on the nutritional status of patients with cystic fibrosis.
- Evaluate the impact of behavioral interventions on the nutritional status of patients with cystic fibrosis.
- Describe the challenges in determining optimal dosing of pancreatic enzyme replacement therapy.

GUEST AUTHORS OF THE MONTH

Commentary & Reviews

Deepak Agrawal, MD
Adult Gastroenterologist
University Texas Southwestern Medical Center
Dallas, Texas

Sarah Jane Schwarzenberg, MD
Pediatric Gastroenterologist
University of Minnesota Masonic Children's Hospital
Minneapolis, Minnesota

Guest Faculty Disclosure

Drs. Deepak Agrawal and Sarah Jane Schwarzenberg and and indicate they have no financial interests or relationships with any commercial entity whose products or services are relevant to the content of this presentation.

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The authors indicate there will be no off-label or unapproved uses of any drugs or products.

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The Johns Hopkins University
Baltimore, Maryland

Suzanne Sullivan, RN, BSN
Senior Clinical Nurse
Johns Hopkins Hospital
Baltimore, Maryland

COMMENTARY

Almost 85% of patients with cystic fibrosis develop pancreatic insufficiency. The normal pancreas secretes most of the lipase necessary to digest fats; thus pancreatic insufficiency often results in malabsorption of fat and fat-soluble vitamins. In these situations, oral pancreatic enzyme replacement therapy (PERT) is given. The goal of PERT is to restore normal fat absorption by delivering "a sufficient amount of active lipase at the right place and at the right time."[1] Use of oral pancreatic enzymes was reported as early as the 19th century, but as most enzymes were destroyed by stomach acid, efficacy was limited. Despite significant improvement and standardization of formulations and the availability of acid reducing medications, optimal dosing of pancreatic enzymes continues to remain a challenge. Most PERT available in the United States is formulated as microbeads or microspheres and is enteric coated. However, a nonenteric-coated enzyme was approved in 2012.

Normally the pancreas secretes 9,000 to 18,000 units/min of lipase with each meal.[2] The pancreas has a large functional capacity and only 5%-10% of normal output is necessary for adequate absorption of ingested fat.[3] Early studies with uncoated pancreatic enzymes showed that a dose of 30,000 lipase units with a meal could abolish steatorrhea if the gastric pH was not too low.[4] Increasing dosages of uncoated enzymes without neutralizing the gastric acidity did not increase fat digestion, as lipase is inactivated at pH ≤ 4. Enteric-coated pancreatic enzymes that release the enzymes only at a pH of 5-6 (and are thus not inactivated by stomach acid) were a major improvement in PERT, with initial studies showing significant improvement in steatorrhea with only 18,000 units/meal.[5]

However, in practice, achieving an adequate clinical response to PERT remains a challenge. Among the proposed reasons for an inadequate response to PERT are insufficient dosage; low pH in the duodenum, which results in incomplete release of enzymes from the microbeads; differential gastric emptying of microbeads and food; and/or rapid small-intestinal transit, which reduces mucosal contact time. Although not a subject of this discussion, nonpancreatic factors leading to maldigestion and malabsorption should also be considered.

Guidelines suggest an initial PERT dose of 500-1000 lipase units/kg/ meal.[6,7] Adjusting the initial dosage of PERT to correspond to grams of fat in the diet has also been recommended, but practically is more difficult to use. When PERT response is suboptimal, the options include increasing the dose of enzymes, adding antisecretory drugs to decrease production of gastric acid, or changing the enzyme formulation.

Increasing the dose is often a reflex reaction, and guidelines allow dosing up to 2000 lipase units/kg/meal — but studies suggest this may not be the optimal strategy. For example:

- A randomized, double blinded, two-way crossover study compared two doses of enteric coated PERT (10,000 units or 20,000 units with each meal). Both groups

received acid inhibition with proton pump inhibitors. No differences in fat excretion or symptoms scores were seen in the two groups.[8]

- Another randomized, double-blinded study compared the effect of two doses of an enteric-coated pancreatic enzyme (140,000 vs 35,000 lipase units per day) on coefficient of fat absorption (CFA) in patients with chronic pancreatitis.[9] The higher dose was within the range of recommended doses, while the lower dose was not expected to have any effect. However, both the low and high doses produced similar improvement in CFA, including increase body weight and BMI. In a post-hoc analysis, patients with severe pancreatic insufficiency (CFA < 65%) had better fat absorption when given higher doses of the enzyme.
- A randomized crossover study compared two doses of enteric-coated pancreatic enzymes with and without omeprazole in patients with pancreatic insufficiency and steatorrhea due to cystic fibrosis. Increasing the dose of enzymes did not produce further improvement in steatorrhea. Addition of omeprazole, however, improved symptoms.[10]

Current recommended dosing, primarily based on trials designed to obtain regulatory approval, compared pancreatic enzymes with placebos. Hence, the actual clinical effective doses may cover a wide range. The maximum recommended doses of PERT (regardless of enzyme preparation) is 10,000 lipase units/kg/day.[6,7] This maximum dose was selected because of concerns about fibrosing colonopathy, a complication thought to be associated with exposure to high amounts of PERT. However, clinical studies are needed to determine optimal dosing.

The second option often tried in patients with an incomplete response to enteric-coated PERT is addition of antisecretory drugs (proton pump inhibitors and histamine-2 receptor blockers) to reduce gastric acidity. Enteric-coated pancreatic enzymes should not be affected by low gastric pH, but persistent duodenal acidity due to lack of bicarbonate secretion in people with CF is thought to inhibit dissolution of the enteric coat in the duodenum.[11,12] As suggested in a seminal 1991 study by Heijerman,[10] neutralization of duodenal contents could explain the beneficial effects of adding omeprazole to enteric-coated PERT in patients with CF. However, other studies have not shown the same benefit. Currently, routine use of adjuvant proton pump inhibitor therapy to increase effect of enteric-coated PERT is not standard treatment, but it is suggested when maximal enzyme dosing is not effective. One FDA approved preparation of PERT contains pancrealipase and sodium bicarbonate. In a single, small, randomized, controlled trial, that preparation significantly improved coefficient of fat absorption over placebo.[13]

The third factor affecting the function of enteric coated PERT is the timing of its availability in the duodenum — is the enteric coating of the enzymes dissolved in time to aid in digestion? Patients with pancreatic insufficiency and CF often have gastrointestinal dysmotility and reduced bicarbonate secretion;[14] the enzymes may not empty from the stomach into the duodenum in time, or the pH may not be high enough for the enteric coating to dissolve. The intestinal dysmotility may push the enzymes distally before effective digestion and absorption. In an interesting (1993) experiment on the fate of orally ingested pancreatic enzymes in pancreatic insufficiency, Guarner et al measured trypsin and lipase activity in the duodenum and ileum in patients with pancreatic steatorrhea vs healthy controls, randomizing subjects to placebo or 40,000 units of enteric coated lipase. Placebo-treated patients with pancreatic steatorrhea had lower enzyme levels in the duodenum than in the ileum. Although PERT significantly decreased steatorrhea, the enzyme levels were found to be greater in the ileum than in the duodenal segment. These results suggest that although enteric-coated PERT improved pancreatic steatorrhea, the ingested lipase and absorptive potential of the small bowel was only partially used.[15] Further, the timing of when pancreatic enzymes are taken — ie, before, during, or after meals — does not appear to make much difference in fat digestion.[16]

Not much is known about the rates of dissolution of microbeads or microspheres within the enteric-coated PERT inside gastrointestinal tract; information about dissolution rates was established using in vitro tests. Lohr et al (2009) investigated the properties of commercially available PERT agents and found a wide variation in the particle size (which determines pyloric passage), specific surface area, and release kinetics of lipase activity at pH 6 in the duodenum.[17] The differences in physical properties between different PERT products (which can affect the kinetics of enzyme release) may explain why one product may show better results than the other in an individual patient.

In difficult cases, combination of uncoated and enteric-coated PERT may be tried. Uncoated enzymes mix well with the meal and initially provide high duodenal lipase activity for early fat digestion (provided the patient is also taking antisecretory medications to raise pH and prevent inactivation of the uncoated enzymes). Taking enteric-coated pancreatic enzymes later could theoretically provide enzymes as the stomach starts emptying contents into the duodenum.[18] No large or randomized studies have been done to validate this approach.

Clinicians often ask how to determine if they are using the optimal dose of PERT. What should inform them that the dosing needs to be adjusted? Should they follow symptoms (fatty diarrhea, bloating, abdominal discomfort), caloric intake, increase in weight (and height for children) or improvement in laboratory parameters (fat soluble vitamin levels)? The answer may differ for individual patients, depending on goals of care. For example, abdominal symptoms may not be just due to fat malabsorption but to other conditions that are prevalent in cystic fibrosis, such as constipation and bacterial overgrowth. Furthermore, increasing the dosages of PERT may improve fat absorption but may not eliminate steatorrhea.[19,20] Although there have been several tests suggested to assess functional efficacy of PERT, none are in widespread use, and each has significant problems with accuracy and effect of other gastrointestinal disease.

In children taking PERT who continue to have poor nutrition, it is important to review compliance with treatment. In a recent study, children who were > 50% adherent to enzymes showed significantly more weight gain in three months than children who were < 33% adherent.[21] In addition, understanding the social situation, the child's behavior, and the family's dynamics is also very important. Mealtime behaviors such as choice of food, time taken to complete meals, and prompting can make a significant difference in number of calories consumed. In the study by Powers et al (reviewed in this issue), targeted behavioral treatment and parental counseling helped children achieve target recommended intake.[22] Further, caring for children with CF can be overwhelming for families; mood disorders have been identified in 33%-50% of caregiving parents.[23] As described in the study by Baker and Quittner (reviewed herein), children whose parents have depressive symptoms are much less likely to adhere to PERT and have less weight gain.[21]

Finally, the new disease modifying therapies in cystic fibrosis such as ivacaftor (as detailed in reviewed the article by Borowitz et al) have been found to improve nutritional status and growth parameters.[24] As research into this area expands, the current over-reliance on PERT as the primary means to improve nutrition may change in future.

In conclusion, PERT dosing must be individualized. The guideline of 500 lipase units/kg/meal to 1,000 lipase units/kg/meal is a good starting point, but the doses will have to be adjusted. If there is poor response to PERT, clinicians should first ensure that the patients are taking the enzymes with or during meals. Sometimes adherence barriers are related to child's mealtime behavior, and behavioral therapy for preschool-aged children with CF can be quite successful in these situations. Other things to consider to increase response to PERT include adding proton pump inhibitors or H2 blockers to decrease gastric acid production, changing the formulation, and/or increasing the dose. Clinicians should keep in mind that the recommended maximum levels of 2,500 lipase units/kg/meal or 10,000 lipase units/kg/ day of lipase are empiric; and if needed, higher doses may be prescribed. However, few patients should require such high doses.

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Improvement in Nutritional Status with Ivacaftor

Borowitz D, Lubarsky B, Wilschanski M, et al. Nutritional status improved in cystic fibrosis patients with the G551D Mutation after treatment with ivacaftor. *Dig Dis Sci*. 2016 Jan;61(1):198-207.

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Ivacaftor is a cystic fibrosis (CF) transmembrane conductance regulator (CFTR) potentiator; in individuals with the G551D gating mutation, ivacaftor therapy improves pulmonary function by increasing the channel-open probability.[1] Improved pulmonary function was shown in phase III studies.[2,3] In this paper, Borowitz et al analyzed the data from these studies to explore improvement in weight and body mass index (BMI) after 48 weeks of ivacaftor treatment in people with CF carrying at least one G551D *CFTR* mutation.[4] A total of 213 subjects aged 6 years and older received at least one dose of ivacaftor; 93% reported being pancreatic insufficient. In both adults and children, statistically significant weight gain was seen as early as two weeks into ivacaftor treatment, compared to placebo. Both age groups demonstrated significant increases in BMI over the 48-week trial. There was not significant improvement in height in children who received ivacaftor, compared to placebo, perhaps because the study period was too short to demonstrate improvements in this measure. Quality of life improvements were also seen in eating, digestive health, body image, and weight domains (as measured by the CF-Questionnaire-Revised version 2).

The reasons for improved weight and BMI in individuals with gating mutations has been speculated although not proven. Improved lung function, demonstrated as improved FEV_1 percent predicted with ivacaftor treatment, may reduce work of breathing and thus resting energy expenditure (REE). In the studies thus far, there was no correlation between weight gain and FEV_1 percent predicted, and REE was not directly measured. Direct measure of the timing of gastric acid neutralization in the intestine in subjects treated with ivacaftor compared to placebo shows that the treated subjects have early neutralization, more similar to that in normal individuals.[5] Higher intestinal pH promotes digestion and absorption of food, which might suggest a mechanism for improved weight gain with ivacaftor.

Improved nutritional status is linked to improved survival in CF. The effect of ivacaftor on growth may both improve the quality of life of individuals with CF and contribute to improved survival.

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Impact of Behavioral Interventions on Nutritional Status

Powers SW, Stark LJ, Chamberlin LA, et al. Behavioral and nutritional treatment for preschool-aged children with cystic fibrosis: a randomized clinical trial. *JAMA Pediatr*. 2015 May;169(5):e150636.

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Better nutritional status in early childhood has been associated with improved clinical outcomes and survival in patients with cystic fibrosis. Children and parents are advised to assure intake of 20%–50% more calories compared to children without CF. Parental involvement is the key to successful nutritional outcomes, and great emphasis has been placed in educating parents about nutrition — why, what, and when to eat. This approach has helped, but families often find it difficult to follow the recommendations, with one of the most common barriers being challenging mealtime behavior.

Behavioral factors such as mealtime duration, family mealtime interactions, and child mealtime behaviors limit dietary adherence in children with CF. In a prior single center study, it was shown that after behavioral and nutrition intervention (BEH), children were able to meet the energy intake recommendations and maintain these gains up to 12 months after treatment.[1] In this 2015 study, Powers and colleagues tested the BEH approach in children 2 to 6 years old, in a randomized, controlled, multicenter trial. The investigators designed a behavioral intervention that combined individualized nutritional counseling targeting increased energy intake with training in behavioral child management skills. Postdoctoral psychology fellows conducted the BEH sessions using a structured treatment manual. Fellows were trained and supervised by a licensed clinical psychologist with specialized experience in behavioral management. The control arm provided education and served as a behavioral placebo, controlling for attention and contact frequency. Both treatments were delivered in person or by telehealth (telephone). Sessions occurred weekly for eight weeks, then monthly for four months (six months total trial length). Participants then returned to standard care for one year, with 12-month follow-up thereafter.

The investigational BEH treatment improved energy intake significantly by 485 calories per day (compared to 58 calories per day in the control group) ($P < .001$) and met the target of 140% of dietary recommended intake for an active preschool-aged child. The height of the children in the BEH group increased significantly more compared to control group (height z score 0.09 vs -.02, $P = .049$). There was no difference in the weight between the two groups, a fact that was poorly explained, given the increase in energy intake. However, the ability to improve nutritional intake in children with CF through behavioral therapy creates a new opportunity to improve a crucial factor in clinical outcomes.

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Effect of Parental Depression on Adherence in Children with CF

Barker DH, Quittner AL. Parental depression and pancreatic enzymes adherence in children with cystic fibrosis. *Pediatrics*. 2016 2016 Feb;137(2):1-9

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Children with CF should consume 120%-150% of the energy requirement of healthy peers, a recommended intake that has been associated with better clinical outcomes and reduced mortality. About 80% of children with CF are pancreatic-insufficient and need to take pancreatic enzyme replacement therapy (PERT) to aid in digestion and absorption of fats.[1] However, adherence to PERT is low, ranging from 27% to 46%.[2] One of the factors associated with low adherence to treatment in children with CF is parental well-being, particularly parental mental health. Parental depression and anxiety are seen in up to one third of parents taking care of children with CF.[3]

In this 2016 study, the authors hypothesized that parental depressive symptoms would result in poorer adherence to PERT, which in turn would lead to poorer weight outcomes in their children with CF. To test their hypothesis, the authors contacted 115 families at three CF centers in Florida. Of the 115 families contacted, 28 declined participation and 87 were randomized to enroll in the study; 83 families in the participant group were prescribed PERT. On the first clinic visit, the children were weighed, the primary caregiver completed the depression measure questionnaire, and the families were provided electronic pill bottles for keeping track of pancreatic enzyme use. The Center for Epidemiologic Studies Depression Scale (CES-D) was used to screen depression. Comprising 20 items, the CES-D assessed depressed mood, fatigue, loss of appetite, and sleep disturbance. The electronic bottles recorded the date and time of each bottle opening, thus providing a measurement of adherence to the treatment. Participants returned for their next scheduled clinic visit three months later; data for bottle openings across the three months were downloaded and children weighed. The number of bottle openings was determined separately for “during school hours” on weekdays and for at home.

Average adherence to PERT was 50%: higher at school (94%) than at home (42%), and higher for toddlers (50.6%) than for school-aged children (37.5%). Regarding reported rates of depression among parents, 30% were found to be in the clinical range, with 18% rated as moderately symptomatic. Children of parents with symptoms of depression vs those without were less adherent (34.8% vs 49%). Average gain in weight across three months was greater in children who were > 50% adherent compared to children who were < 33% adherent.

Findings from this study appear to confirm that caring for children with CF can affect parental well-being. International guidelines now recommend annual screening of parent caregivers for depression and anxiety.[4]

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Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety. *Thorax*. 2016 Jan;71(1):26-34.

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Reconsidering Maximal Daily Dose of Pancreatic Enzymes

Borowitz D, Gelfond D, Maguiness K, Heubi JE, Ramsey B. Maximal daily dose of pancreatic enzyme replacement therapy in infants with cystic fibrosis: a reconsideration. *J Cyst Fibros*. 2013 Dec;12(6):784-5.

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In the early 1990s, numerous cases of fibrosing colonopathy, a severe, destructive inflammatory disease of the colon leading to fibrosis and obstruction, were seen in patients with cystic fibrosis.[1] After an association between treatment with high doses of enteric-coated pancreatic enzyme supplements and the disease was suggested, the recommended dose of pancreatic enzyme replacement therapy (PERT) was capped at 10,000 lipase units/kg/day in Europe and the United States.[2] Although a direct causal relationship with PERT was not proved, few cases of fibrosing colonopathy have been seen since that time.

In this paper, Borowitz et al reviewed the adherence to the PERT upper limit recommendations in infants in clinical practice and considered for their appropriateness. Infant diets are high in fat, whether provided by breast milk or formula. Infants in the first three months of life eat frequently, sometimes every three hours during this period. Appropriate PERT, dosed by gram of fat in the diet, will rise above 10,000 lipase units/kg/day in infants. Data on current clinical practices provided by the CF Patient Registry confirms that many centers provide this higher dose of PERT to infants and to children under one year of age. Doses in some centers may be > 17,000 lipase units/kg/day. Additionally, the authors note the absence of reports of fibrosing colonopathy in infants, both in the 1990s and today.

It seems likely that the 10,000 lipase units/kg/day upper limit, which was set by clinical experience and not directly tested through clinical trial, is too low to provide adequate enzyme therapy to young infants. The period of this higher dose of enzymes is short; children generally reduce the frequency of feeds after three months of age, and as growth velocity is reduced after the first year of life, the higher level of PERT is unlikely to be necessary beyond this period. However, the community of infants with CF would benefit from direct studies of appropriate pancreatic enzyme supplementation dose.

As the benefits of PERT have been shown to outweigh the risks, clinicians should not shy away from increasing the doses of pancreatic enzymes in infants beyond the currently recommended 10,000 lipase units/kg/day.

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KEY TAKEAWAYS

- Treatment of patients with CF with ivacaftor improves not only pulmonary status but also nutritional status.
- Teaching parents about how to deal with CF children's mealtime behavior significantly improves nutritional status.
- Mood disorders such as anxiety and depression are common among parents caring for children with CF and can adversely affect adherence to pancreatic enzyme therapy.

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Respiratory Therapists For United States: Visit this page to confirm that your state will accept the CE Credits gained through this program.

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INTERNET CME/CE POLICY

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STATEMENT OF RESPONSIBILITY

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INTENDED AUDIENCE

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This activity was developed in collaboration with DKBmed.

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Click on link to download instructions for the post-test and evaluation

PHYSICIAN POST-TEST

NURSE POST-TEST