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Nutrition: Prevention and management of nutritional failure in Cystic Fibrosis

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Abstract

Close monitoring of nutritional status is critical to the overall health of a patient with CF. As part of routine CF care, measurement of weight and height (and calculation of weight/length or BMI as appropriate) should be performed and analyzed at each visit. Early recognition of nutritional risk is imperative and evaluation with a multidisciplinary team should be performed to assess for caloric intake, caloric malabsorption, and other causes of poor weight gain and growth. Many tools are available to use for intervention, including oral supplementation, behavioral interventions, medications, nutritional therapies, and enteral tube feeding.

Keywords: Nutrition; Cystic fibrosis; Fat soluble vitamins; Enteral feeding

1. Background

Close monitoring of nutrition and growth is essential in caring for pediatric and adult patients with Cystic Fibrosis (CF) [1]. The Cystic Fibrosis Foundation (CFF) recommends that nutritional status be monitored as part of routine CF care, and that both children and adults with CF achieve nutritional status comparable to healthy children and adults, as optimal nutritional status is associated with better clinical outcomes [2,3]. Despite this knowledge, optimal nutritional status may be difficult to achieve and maintain.

Nutritional status may assessed by weight, height, weight-for-length percentiles (in children <2 years of age), and Body Mass Index (BMI; used in children ≥2 years of age and adults). The CFF recommends performing these parameters every month during the first year of life and then every three months as part of routine CF care, for patients meeting nutritional goals [1]. The frequency of nutritional assessments should increase in clinical scenarios where nutritional status is suboptimal (to every 2 weeks in infants and every 6–8 weeks in children >2 years of age and adults) [1]. Recent guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) discuss limitations of using only weight, length, and BMI or weight-for-length, and suggest supplemental methods to analyze body composition including dual-energy X-ray absorptiometry (DEXA), anthropometrics, and bioelectrical impedence for all patients with CF [4]. Specifically, DEXA is recommended for all patients from 8 to 10 years of age [4].

Focusing on and achieving optimal nutritional status early in life is important. Identifying children with CF early in life through newborn screening leads to improved nutritional status, improved growth, fewer pulmonary exacerbations, and fewer hospital days [5–7]. By age two, weight-for-length >50%ile correlates with improved lung function between ages six

Abbreviations: BMI, Body Mass Index; CDC, Centers for Disease Control and Prevention; CF, Cystic Fibrosis; CFF, Cystic Fibrosis Foundation; CFTR, cystic fibrosis transmembrane conductance regulator; DEXA, dual-energy X-ray absorptiometry; EFA, essential fatty acids; ESPEN, European Society for Clinical Nutrition and Metabolism; FDA, Food and Drug Administration; FEV, forced expiratory volume; GERD, gastroesophageal reflux disease; IBW, ideal body weight; WHO, World Health Organization.

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through fifteen [8], and children who recovered their birth weight z-score by two years of age had improved lung function at six years of age [9]. Weight-for-age percentile at four years of age has been associated with improved height and growth velocity as well as improved survival and fewer pulmonary exacerbations at age eighteen [2]. Continuing this effort into adulthood is essential, as higher BMI in adults with CF has been associated with improved pulmonary function [8].

Current recommendations for nutritional goals vary depending on the age of the patient. For infants and children younger than two years of age, achieving a weight-for-length percentile of ≥ 50% is recommended [8]. This recommendation was based on growth points recorded on the 2000 Centers for Disease Control and Prevention (CDC) growth charts [10]. However, since that recommendation, the American Academy of Pediatrics and the CDC have recommended the use of the 2006 World Health Organization (WHO) growth charts for routine assessment of nutritional and growth status for children less than two years of age [11]. These charts vary significantly, with the WHO growth charts demonstrating higher percentiles for the same weight compared with the CDC growth charts. As such, achieving a weight-for-length of 50th percentile using WHO standards was associated with a lower (but adequate) forced expiratory volume (FEV_1) compared with using CDC standards [12].

For children two years of age and older, achieving BMI percentile ≥ 50% using the CDC growth charts is recommended [8]. For adults older than 20 years of age, the CFF recommends attaining a BMI ≥ 22 kg/m^2 in females and attaining a BMI ≥ 23 kg/m^2 in males [8]. While these recommendations note the importance of achieving an adequate BMI, it is also important to evaluate the overall growth and nutritional status in children. A slowed growth velocity may result in a higher BMI despite the presence of suboptimal nutritional status, and monitoring BMI alone may result in overestimating nutritional status in stunted children [13]. In addition, height is related to lung volumes, and is an important factor to consider in the overall health of the child and adolescent with CF [14,15]. Lastly, the composition of body weight should be considered, as an increased Lean Body Mass Index (LBMI) is more closely associated with improved pulmonary function than BMI, particularly in undernourished children [16]. Thus, achieving a goal BMI by gaining muscle mass (and not by gaining visceral fat mass) is important.

The CFF has published several guidelines with critical information and guidance on the diagnosis and management of malnutrition. In 2002, the CFF and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, convened a team of experts to determine guidelines for the timing and composition of nutritional assessments in children with CF, including anthropometric measurements and macro- and micronutrient requirements, the evaluation of patients with nutritional failure, and strategies for improving nutritional status [1]. In 2008, the CFF revised these recommendations to improve classification of nutritional risk through analysis of the CFF Patient Registry and reviewing current literature [8]. The 2009 infant care guidelines, developed by the CFF, recommend increasing caloric intake, considering micronutrient deficiencies, and using behavioral interventions to improve weight gain in infants and young children with suboptimal nutritional status [17]. In 2016, clinical practice guidelines for preschoolers with CF were developed through the CFF [18]. While these recommendations inform the management of pulmonary disease, much of the recommendations are focused on nutrition and gastrointestinal complications of CF. Specifically, these guidelines recommend an algorithm for the management of nutritional status (including anthropometric assessment, determination of nutritional risk, further evaluation for co-morbidities, and treatment of nutritional failure). Most recently, also in 2016, evidence-informed guidelines for the use of enteral tube feedings in children and adults with CF were published, with emphasis on indications and contraindications for placement of feeding devices, perioperative management of feeding devices, and long-term follow up for enteral devices [19]. Internationally, the Dietitians Association of Australia National Cystic Fibrosis Interest Group published Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis [20], and ESPEN (with collaboration from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Cystic Fibrosis Society) published guidelines in 2016 on nutrition care for pediatric and adult patients with CF [4].

2. Clinical presentation and differential diagnosis

In the 2002 consensus report on nutrition for pediatric patients, nutritional failure was defined as height <5%ile for age, ideal body weight (IBW) <90%ile for age, weight-for-length <10%ile for age (in children and infants younger than two years of age), and BMI <10%ile for age (in children two years and older) [1]. At-risk nutritional status was defined as height %ile less than genetic potential, IBW 10–25%ile for age, weight-for-length 10–25%ile for age (in children and infants younger than 2 years of age), and BMI 10–25%ile for age (in children two years and older) [1]. Based on evidence linking BMI and FEV_1, nutritional guidelines were updated in 2008 [8]. In addition to these BMI goals, the most recent nutritional guidelines for preschoolers with CF recommend attaining a weight for-age ≥ 10%ile, accounting for evidence that achieving weight ≥ 10%ile at age four is associated with improved survival at age 18 [2,18]. Table 1 summarizes current CFF recommendations for nutritional goals.

Patients with CF and their families should be educated about the importance of nutritional care throughout the life span of the patient with CF [19]. Reviewing diet history every 3–6 months is recommended [4]. However, when a patient is not able to attain the nutritional goals recommended by the CFF, interventions should begin early, and all options should be

Table 1
Summary of Nutritional Goals as Recommended by the Cystic Fibrosis Foundation [2,8,18].

Age	Guideline
<2 years	Weight-for-length ≥ 50%ile for age
2–5 years	BMI ≥ 50%ile for age
	Weight ≥ 10%ile
>5–18 years	BMI ≥ 50%ile for age
>18 years (female)	BMI ≥ 22 kg/m^2
>18 years (male)	BMI ≥ 23 kg/m^2

discussed with the patient and family. Ongoing education of the multiple tools and choices available to improve nutritional status is important in order for the patient and family to fully participate in the decision-making process. It is critical to recognize that it can take time for patients and families to become comfortable with the use of more invasive interventions, including gastrostomy tubes [21].

Initial assessment of the child at nutritional risk should include determination of caloric intake (diet history), presence of malabsorption (presence of steatorrhea, history of pancreatic enzyme administration), and if a pulmonary exacerbation is present [1,18]. Identifiable causes should initially be addressed [1]. Insufficient caloric intake may be diagnosed with a diet diary by a registered dietitian/nutritionist and the patient should be counseled to maximize energy intake [1,18]. These dietary recommendations should be tailored to each individual patient with CF [4]. Generally, diets high in fat are recommended for patients with CF. They types of fat ingested should be considered, as encouraging intake of monounsaturated and polyunsaturated fats (versus saturated fats) may be beneficial [22].

3. Diagnostic workup

If the patient's nutritional status remains at risk, it is important to employ a multidisciplinary team with expertise in CF [18,19]. This team should ideally consist of a pulmonologist, registered dietitian/nutritionist, gastroenterologist, endocrinologist, psychologist, nurse, social worker, and respiratory and/or physical therapist, as well as the primary care provider [18,19]. At this point, investigations should begin, looking into other co-morbidities that may result in suboptimal nutritional status. Nutrition counseling, with an experienced dietitian should continue with obtaining a diet history and encouraging a high fat diet [20]. Foods high in linoleic and other long chain polyunsaturated fatty acids could be considered [4]. Discussion should continue around use of enteral tube feeding as an option for treatment. A gastroenterologist should be involved to evaluate for CF-related gastrointestinal causes that result in poor appetite and/or increased intestinal losses including malabsorption, small bowel bacterial overgrowth, gastroesophageal reflux disease, constipation, and CF-related liver disease. There may be an increased risk of gastrointestinal diseases in patients with CF, thus other gastrointestinal diseases should also be considered, including eosinophilic gastrointestinal disease, celiac disease, motility disorders, and inflammatory bowel disease [23]. CF-related diabetes mellitus and impaired glucose tolerance can contribute to suboptimal nutritional status, and an abnormal oral glucose tolerance test should prompt referral to an endocrinologist [1,18]. Psychologists and behavioral therapists are critical to the multidisciplinary team as they can assess for psychosocial causes of suboptimal nutritional status, including depression, anxiety, body image disorders, and anorexia nervosa [4,18,19]. Social workers and nurse coordinators should assess for financial instability or other social stressors that could contribute to suboptimal nutritional status [18,19]. Table 2 summarizes commonly encountered causes of nutritional failure in patients with CF.

Table 2
Potential Causes of Nutritional Failure to Consider in Patients with Cystic Fibrosis.

Discipline	Team member	Potential cause/co-morbidity
Pulmonary	Pulmonologist	Pulmonary exacerbation
Nutritional	Dietitian	Insufficient caloric intake
Gastrointestinal	Gastroenterologist	Pancreatic insufficiency
		Small bowel bacterial overgrowth
		Gastroesophageal reflux disease (GERD)
		Eosinophilic gastrointestinal disease
		Celiac disease
		Motility disorders
		Constipation
		Inflammatory bowel disease
		CF-related liver disease
Endocrine	Endocrinologist	CF-related diabetes mellitus/impaired glucose intolerance
Psychosocial	Social Worker	Food insecurity
	Psychologist	Depression/anxiety
		Body image disorders
		Anorexia nervosa

4. Routine management

4.1. Oral supplementation

At the same time the CF multidisciplinary team is looking at other causes of suboptimal nutritional status, the team should also begin interventions, as clinically indicated, to improve caloric intake. While increasing caloric intake with high-calorie and fat foods and oral supplementation is recommended [1,4,17,18], it may not be sufficient to improve nutritional status [24–26].

4.2. Behavioral therapy

Disordered eating behaviors can affect nutritional status, and behavioral therapy may be indictated for some children and adults with CF who have suboptimal nutritional status. In toddlers and preschool-aged children with CF, behavioral feeding problems are commonly encountered and can interfere with attaining optimal nutritional status [27–29]. Targeted behavioral feeding therapy has been shown to be superior than standard nutritional care in young children with CF in improving overall caloric intake and height z-score [30]. Based on this knowledge, the CFF recommends that parents compliment appropriate eating behaviors, pay minimal attention to behaviors not compatible with eating, and limit meal times to fifteen minutes with snacks or "mini-meals" occuring at discrete times between meals, and involving a behavioral therapist to assist with individualizing interventions [8,17,18]. In adolescents and adults with CF, body image may negatively affect nutritional intake [31,32]. These factors are important to note and, if present, treat, as increasing interventions (specifically, using enteral nutrition) can negatively affect quality of life in some adolescents and adults with CF [32]. Interestingly, early education of patients and families/caregivers about enteral nutrition may result in improved outcomes and participation in the decision for enteral nutrition [21]. The CFF recommends introduction of enteral

nutrition early and that enteral nutrition be offered as a tool to improve nutritional status, as opposed to a last alternative [19].

4.3. Medications

Appetite stimulants may be considered to improve caloric intake in children and adults with suboptimal nutritional status that is related to insufficient caloric intake. Appetite stimulants are mentioned as options to consider in the child with CF and poor nutritional status in CFF guidelines, however ESPEN could not offer an evidence-based recommendation due to lack of high quality evidence [4,18]. The most commonly encountered appetite stimulants used in the CF population are cyproheptadine, megestrol acetate, and dronabinol. Cyproheptadine is an antihistamine, with a secondary effect of appetite stimulation. While its mechanism of action as an appetite stimulant is unknown, cyproheptadine is generally well-tolerated with the exception of transient drowsiness at the onset of therapy. The effect on weight may be modest and short-lived, as most effects occur in the first few months of therapy [33–35]. Megestrol acetate is a derivative of progesterone with a secondary effect of appetite stimulation and weight gain. While the mechanism of this drug is also unclear, it has also been used successfully in patients with AIDS and cancer. Side effects are possible including adrenal suppression and diabetes [33]. Dronabinol is an oral form of delta-9-tetrahydrocannabinol and is the principal psychoactive substatnce present in marijuana. Limited data in CF have demonstrated improvement in weight with effects on mood and cognition (including euphoria, hallucinations and lethargy) reported [33].

For patients with pancreatic insufficiency and suboptimal nutritional status, pancreatic enzyme administration should be optimized as part of routine management. Adminstration of pancreatic enzymes is addressed in the article on pancreatic insufficiency by Singh and Schwarzenberg in this supplement [36].

Specific nutritional therapies, including sodium, zinc, and essential fatty acids, have been explored as factors playing a role in suboptimal nutritional status.

4.3.1. Sodium

Sodium supplementation is critical in the management of patients with CF, as excessive salt loss occurs through the skin. Sodium loss can lead to hyponatremic dehydration in infants and can contribute to poor weight gain [37,38]. As a result, the CFF recommends supplementing sodium (as sodium chloride) in infants. Infants younger than 6 months of age should take 0.125 tsp. of sodium chloride daily, and infants 6 months and older (and children with a low salt diet) should take 0.25 tsp. sodium chloride daily [17,18]. In addition, older children and adults in warm environments or while exercising should supplemented with salted sports drinks (0.125 tsp. sodium chloride added to 12 oz. sports drink) to avoid hyponatremia [39]. ESPEN guidelines suggest adding 1–2 mmol/kg/day of sodium in breastfed infants, up to 4 mmol/kg/day in infants with increased sodium losses, and salty food intake in older children and adults [4]. ESPEN guidelines also recommended assessing the need for sodium supplementation by obtaining a urinary sodium:creatinine ratio [4].

4.3.2. Zinc

Zinc is an important micronutrient for growth and immunity, and patients with CF are at risk for zinc deficiency as fat malasorption can negatively affect zinc absorption [40]. Given that zinc deficiency can result in poor growth, the CFF recommends empiric zinc supplementation for 6 months (1 mg elemental zinc/kg/day in divided doses) in infants and children with poor growth [1,17] ESPEN guidelines suggest zinc supplementation for patients with CF who are at risk for zinc deficiency [4].

4.3.3. Essential fatty acids

Essential fatty acids (EFA) are fatty acids which must be ingested through dietary sources, as humans are unable to synthesize EFA. These include linoleic acid (the essential omega-6 polyunsaturated fatty acid) and alpha-linolenic acid (the essential omega-3 polyunsaturated fatty acid) which are found in diets rich in vegetable oils and cold-water fish. Alpha-linolenic acid is further metabolized to eocosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), while linoleic acid is further metabolized to arachidonic acid and di-homo-gamma-linolenic acid. EFA deficiency, more common in individuals with pancreatic insufficiency, may present with growth failure, dermatitis, alopecia, and/or thrombocytopenia. The CFF recommends consideration and treatment of EFA deficiency in individuals with suboptimal weight gain [1,17].

4.3.4. Glutathione

Antioxidant therapy, specifically glutathione, will be studied in a multi-center trial commencing in 2017, investigating the effect of glutathione on nutrition and growth in pediatric patients with CF.

4.3.5. Growth hormone

A recent Cochrane review analyzed four controlled trials in patients with CF, demonstrating improvement in growth parameters (height, weight, and lean tissue mass) [41]. While one of the four studies demonstrated improvement in pulmonary function, this finding was not consistent across all studies. Thus, longer term studies are suggested before recommending routine use of growth hormone in patients with CF [41].

4.3.6. Cystic fibrosis transmembrane conductance regulator (CFTR) modulators

A randomized, double-blind, placebo-controlled study of lumacaftor/ivacaftor administered over 24 weeks demonstrated improvements in BMI z-score in the lumacaftor/ivacaftor group compared to placebo [42]. An open-label phase 3 study of lumicaftor/ivacaftor administered over 24 weeks led to improved BMI z-score in children ages 6–11 years with CF homozygous for F508del [43]. Ivacaftor, administered over 48 weeks, improved weight z-score and BMI z-score compared to placebo in subjects older than 6 years of age with at least one G551D mutation [44]. Thus, nutritional status may improve as CFTR modulators are used with increased frequency.

4.4. Enteral tube feeding

The use of enteral nutrition, specifically supplementation provided via nasogastric tubes, gastrostomy tubes, or gastro-jejunal tubes, is an important tool in the management of nutritional failure, as enteral feeding improves nutritional and growth status in children and adults with CF [20,21,45–50]. Enteral nutrition should be discussed throughout the lifetime of the individual with CF and not viewed as a "last resort [19]". The CFF recommends use of enteral tube feeding to improve anthropometrics when unable to attain caloric intake despite evaluation by a multidisciplinary CF team [19]. ESPEN recommends initiation of enteral tube feeding in the presence of persistent failure to thrive (weight and length < 10%ile) [4]. Involvement of a multidisciplinary team is important, as assessment by this type of team has been shown to improve post-gastrostomy tube placement mortality [51]. Early discussion of enteral tube feeding can allow an individual with CF and his/her caregivers ample time to become comfortable with the decision to pursue enteral tube feeding [21]. A survey of providers and patients and families prior to gastrostomy tube placement demonstrated a lack of understanding in patients and families prior to gastrostomy tube placement. Not surprisingly, patients without a gastrostomy tube perceived more discomfort and had more aesthetic concerns than patients with a gastrostomy tube [52]. Thus, allowing for ample time and providing improved patient/caregiver education around enteral tube feeding is recommended prior to enteral tube placement [19].

Nasogastric tubes may be an option for some children and adults with CF. These feeding devices are recommended for short term nutritional rehabilitation (< 3 months), as complications including tube dislodgement, bleeding, nasal erosion may occur [19]. In addition, the presence of nasal polyps may complicate placement [53]. Some patients may prefer intermittent nasogastric feeds, and this should be considered in the appropriate clinical scenario.

Gastrostomy tubes are the most commonly placed enteral feeding device. These feeding devices may be placed by different techniques: percutaneous endoscopic gastrostomy, laparoscopic gastrostomy, or radiologic technique. Open surgical technique is recommended when there are contraindications to the less invasive techniques [19]. While enteral nutrition through a gastrostomy tube may be administered as a bolus or a continuous rate, the CFF recommends nighttime continuous nocturnal infusions of enteral nutrition [19]. This may allow for improved consumption of oral calories during the day.

Jejunal or Gastro-jejunal tubes may be indicated in patients with severe gastroesophageal reflux disease, significant gastroparesis, or pancreatitis. When enteral nutrition is administered directly into the jejunum, continuous feedings are required. Clogging, perforation, and displacement can occur with jejunal tubes. When malfunctioning, these feeding devices require replacement, generally with a radiographic technique. Finally, feedings need to be administered by continuous feeding over many hours during the day, thus may be inconvenient for the patient and/or caregiver [19].

4.5. Formula selection and enzyme administration

In infants, human milk (if available) and standard infant formulas should be used unless intolerance is noted. Human milk, as available, is recommended as the initial type of feeding for infants with CF, and may have benefits over formula [17,54]. Caloric density of the selected feeding may be increased to attain improved nutritional status [17,19]. For children older than 2, the multidisciplinary team should determine the needs of the patient on an individual basis, as there is insufficient evidence to support one specific type of formula (polymeric, semi-elemental, elemental) [19]. ESPEN guidelines suggest using semi-elemental formula in patients not tolerating polymeric feeds [4]. Evidence is also lacking regarding specific methods of pancreatic enzyme replacement therapy during continuous feedings [19]. The most common method of pancreatic enzyme administration is to provide enzymes before and after enteral feeds (and during the middle of the night if the patient wakes from sleep) [4,55]. An inline cartridge lipase delivery system has recently been approved by the FDA for adult patients, which may allow for continuous digestion of fat during continous nocturnal feedings. In a study of 33 adult and pediatric patients with pancreatic insufficiency, using the inline cartridge improved markers of fat absorption, GI symptoms, and morning appetite [56].

4.6. Parenteral nutrition

Parenteral nutrition, while not routinely recommended for sole nutritional support in patients with CF, should be used in instances where enteral nutrition is contraindicated (bowel resection, infant with meconium ileus, or other causes of intestinal failure) [4,57]. There may be significant risks associated with administration of parenteral nutrition, including need for central venous access, infection, and cost [58].

5. Potential endpoints for testing therapies in clinical trials

There is much to learn about nutritional supplementation in children and adults with CF. While there is a well-documented association between improved BMI percentile and lung function, studies observing patients receiving enteral nutrition have had mixed results with only some studies noting improved lung function [19,47,50,59–63]. Many of the studies are retrospective and involve children and adults with end-stage CF. A recent Cochrane review was unable to include any trials to date regarding the effects of enteral feeding in patients with CF; therefore it was recommended that new trials be commenced to understand when enteral nutrition should be initiated for the best results [64].

We would suggest the following outcomes be considered when assessing efficacy of a therapy or intervention on nutritional status:

- height z-score (and mid-parental height)
- weight z-score
- wt/length z-score (in children under 2)
- BMI %ile (children 2–18)

- BMI (adults >18)
- micronutrient status
- essential fatty acid status and long chain polyunsaturated fatty acid (PUFA) levels
- caloric and fat intake
- quality of life
- pulmonary status, including FEV1.

6. Future directions

There remain many questions as to how to improve nutritional status in children and adults with CF, including:

- Which type of formula is most efficacious?
- How should enzymes be administered during enteral tube feeding?
- How to alter mealtime behaviors in young children and body image in adolescents to improve adherence to a nutritional plan?
- What will be the effect of CFTR modulators on nutritional status and growth in children?
- Is there a role for other micronutritients or essential fatty acids as therapy to improve nutritional status?

7. Clinical practice points

- Routine monitoring of growth and nutritional status is essential.
- Recognition of patients at risk for or in nutritional failure should prompt a multi-disciplinary evaluation of nutritional status and for potential causes of malnutrition or poor growth.
- Aggressive nutritional intervention (including enteral tube feeding) may be critical to help patients achieve the recommended nutritional goals as outlined by the CFF.

8. Summary

Routine assessment of nutritional status is critical in patients with CF. Early recognition of at risk nutritional status or nutritional failure allows for early intervention and improvement of nutritional parameters. A multidisciplinary evaluation is recommended to optimize care. Evaluation for CF-related comorbidities and non-CF causes of nutritional failure is important when treating patients in nutritional failure. There are many options available to improve nutritional status, including increasing caloric intake with oral supplementation, the use of appetite stimulants, optimization of pancreatic enzyme replacement therapy, and evaluation for potential macro- and micro-nutrient deficiencies. The use of enteral tube feeding should be discussed and considered early in the process of treatment of nutritional failure. Many questions remain, however, including the long-term effects of CFTR modulators on nutritional status and growth in children, appropriate formula selection and pancreatic enzyme replacement therapy during continuous enteral tube feeding, and if other micronutrients or essential fatty acids may be important treatment options for nutritional failure.

Conflict of interest

The authors declare no conflict of interest.

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