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e-SPEN guideline

ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis

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SUMMARY

Background: Malnutrition is both a frequent feature and a comorbidity of cystic fibrosis (CF), with nutritional status strongly associated with pulmonary function and survival. Nutritional management is therefore standard of care in CF patients. ESPEN, ESPGHAN and ECFS recommended guidelines to cover nutritional management of patients with CF.

Methods: The guidelines were developed by an international multidisciplinary working group in accordance with officially accepted standards. The GRADE system was used for determining grades of evidence and strength of recommendation. Statements were discussed, submitted to Delphi rounds, reviewed by ESPGHAN and ECFS and accepted in an online survey among ESPEN members.

Results: The Working Group recommends that initiation of nutritional management should begin as early as possible after diagnosis, with subsequent regular follow up and patient/family education. Exclusive breast feeding is recommended but if not possible a regular formula is to be used. Energy intake should be adapted to achieve normal weight and height for age. When indicated, pancreatic enzyme and fat soluble vitamin treatment should be introduced early and monitored regularly. Pancreatic sufficient patients should have an annual assessment including fecal pancreatic elastase measurement. Sodium supplementation is recommended and a urinary sodium:creatinine ratio should be measured, corresponding to the fractional excretion of sodium. If iron deficiency is suspected, the underlying inflammation should be addressed. Glucose tolerance testing should be introduced at 10 years of age. Bone mineral density examination should be performed from age 8–10 years. Oral nutritional supplements followed by polymeric enteral tube feeding are recommended when growth or nutritional status is impaired. Zinc supplementation may be considered according to the clinical situation. Further studies are required before essential fatty acids, anti-osteoporotic agents, growth hormone, appetite stimulants and probiotics can be recommended.

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Conclusion: Nutritional care and support should be an integral part of management of CF. Obtaining a normal growth pattern in children and maintaining an adequate nutritional status in adults are major goals of multidisciplinary cystic fibrosis centers.

1. Introduction

1.1. Development of guidelines for cystic fibrosis nutrition care

The European Society for Clinical Nutrition and Metabolism (ESPEN) launched a process of developing updated guidelines on nutrition care for infants, children, and adults with cystic fibrosis (CF). The group included physicians, dietitians, and educators, all experts in the field of cystic fibrosis, as well as the guidelines coordinator (SMS); all are authors of this guideline document.

Recent Cochrane reviews have highlighted a lack of randomized controlled trials examining the effects of nutritional interventions in patients with CF [1–8]. Consistent with these findings, many of our nutrition guidelines are based on consensus expert opinions [9–11]. The experts followed the GRADE method, which was based on determinations of *grade of evidence* and *strength of recommendation*; the methodology is described elsewhere [12]. A meeting was organized in Stockholm, Sweden, in April of 2012. These new guidelines are meant to update the 2002 European consensus guidelines on nutrition for people with cystic fibrosis [11].

Literature search was conducted in the PubMed and Cochrane databases until 2014, using the following terms: cystic fibrosis AND (nutrition* OR diet* OR nourishment OR nutrient OR nutriment OR malnutrition OR malnourishment OR undernourishment OR calorie* OR lipid* OR trace OR vitamin* OR protein* OR taurine OR pancreatic enzyme replacement therapy OR PERT OR fatty OR micronutrient* OR antioxidant* OR probiotic* OR supplement* OR insulin OR enteral OR parenteral OR EN OR TPN OR PN).

The *grade of evidence* was determined by a number of factors, starting with the number and type of research studies [13–17]. Grading from *High* to *Very Low* was used to rate the quality of the underlying evidence and the level of certainty for effect (Table 1) [15]. Highest quality evidence resulted from consistent results in meta-analysis of multiple randomized controlled trials, with the next highest level defined by at least one well-designed randomized controlled trial. Moderate and low-level evidence came from controlled trials that were not randomized, from cohort- or case-controlled studies, or from multiple time series trials. Very low-level evidence was from expert clinical experience or from descriptive studies. The grade was then decreased if there were limitations to study quality, inconsistencies in findings, imprecise or sparse data, or high likelihood of reporting bias. The grade was increased if there was high consistency of findings or strong evidence of association (Table 1).

The *strength of recommendation* was based on a consensus discussion, which included expression and deliberation of expert opinions, risk-benefit of recommendation, costs, and a review of supportive evidence, followed by Delphi rounds and votes until agreement was reached (Table 2).

Last, a list of all statements was sent to all 2639 ESPEN members with an e-mail address on file to ask for approval/disapproval of every statement, and in the latter case to provide justification. 50 ESPEN members completed the survey, with approval ratings ranging from 61% to 100%. Comments based on the literature were taken into account in the final version of the manuscript. The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the European Cystic Fibrosis Society (ECFS), who are partners of these guidelines, reviewed the final manuscript, with an external review for ESPGHAN.

It is noteworthy to mention than this initiative followed the rules for ESPEN guidelines [12], while based on their own rules ESPGHAN and ECFS qualify it as a position paper.

1.2. Nutrition needs with cystic fibrosis

1.2.1. Statement of the problem: cystic fibrosis and undernutrition

Cystic fibrosis (CF) is a life-threatening genetic disorder that occurs primarily in Caucasians but can occur in other races or ethnicities as well [18,19]. The incidence of CF is about one in 3500 white births in Europe [20]. The mean prevalence in the United States (US) and the European Union (EU) is similar, 0.74 and 0.80 in 10,000 persons, respectively [21].

The CF phenotype results from mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which results in CFTR deficiency or dysfunction, changes that disable the transport of sodium and chloride ions across epithelial and other cell membranes [22,23]. As a result, fluid transport is abnormal, and mucous secretions become thickened, ultimately impairing function of organs such as the lungs and pancreas, as well as the liver, gallbladder and intestines [18,23]. In the lungs, thickened mucus adheres to airway surfaces, which leads to decreased mucociliary clearance, and increased risk for inflammation and infection. In the pancreas, thickened secretions obstruct intra-pancreatic ducts, reducing delivery of digestive enzymes to the intestines and impairing absorption of key nutrients [23].

Table 2
Strength of recommendation.

Strength of recommendation	
Strong	We recommend/do not recommend
Weak	We suggest/do not suggest

Table 1
Grades of evidence.

Level	Definitions of evidence [15]
High	Further research is unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

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Cystic fibrosis is strongly associated with poor nutritional status—linked directly by factors related to the underlying genetic mutation, as well as indirectly by factors such as higher energy needs, energy losses, greater essential fatty acid (EFA) turnover, and decreased nutrient intake and absorption [18,23–26]. In children, poor nutritional status results in stunted growth and development [27]. In children and adults with CF, declining lung function is associated with decreasing nutritional status, leading to increased mortality [28,29]. On the other hand, there is a clear link between good nutritional status and better lung function, which improves clinical outcomes and survival [18,24,28]. Though the nutritional status of CF patients has improved markedly over the past two decades, adequate nutrition still remains a major problem for some [30]. Those who are diagnosed early through newborn screening programmes benefit from earlier intervention. This gives the opportunity to minimize nutritional deficits and is associated with positive nutritional outcomes.

1.2.2. Call to action

To achieve the best possible outcome for each CF patient, it is important to provide care that includes attention to nutrition. To that end, a team of experts—representing ESPEN, ESPGHAN and ECFS—systematically reviewed the medical literature to summarize current knowledge on epidemiology and pathophysiology, prevention, and treatment of CF-related undernutrition. The ESPEN-ESPGHAN-ECFS group then recommended evidence-based guidelines on nutrition care for infants, children, and adults with CF.

1.3. Background on undernutrition in people with CF

Undernutrition in CF results from a mismatch between energy needs and actual food intake, complicated by malabsorption. To date, a high-calorie, high-fat diet with pancreatic enzyme replacement therapy (PERT) and fat-soluble vitamin supplementation has been considered the standard of nutritional care for CF [27]. Newer studies suggest recommendations are also needed for increased intake of protein in order to maintain lean body mass and improve long-term outcomes [24]. Similarly, evidence suggests increased intake of EFA, such as linoleic acid, may be a way to improve survival and growth [31].

1.3.1. Traditional definition of adequate nutrition with CF

For infants and children with CF, nutrition is considered adequate when growth is similar to that of an age-matched non-CF population. For CF adults, the threshold is a specific body mass index (BMI) goal for women and men [32].

However, in older children and adults with CF, a focus on BMI targets alone does not fully define nutritional status. Engelen and colleagues raised concerns about the increasing prevalence of overweight and obesity as a confounding factor to understanding nutritional status [24,33]. That is, increased weight does not necessarily correlate with better lung function; high fat mass but low lean body (muscle) mass in fact predicts poor CF disease prognosis. Thus, future CF nutrition guidelines need to qualify BMI thresholds of adequacy with corresponding thresholds for lean body mass.

1.3.2. Prevalence of CF undernutrition

While increasingly more people in the CF population are achieving adequate nutritional status, undernourishment still persists. According to the most recent European Cystic Fibrosis Society (ECFS) Patient Registry (2010 data) [34], nearly half of all children and adults with CF met nutritional targets in most European countries. That means, however, that about half did not achieve adequate nutritional status. Similar trends are found in the US, where median *BMI percentiles* for age in children with CF increased from 41.0 in 2001 to 51.3 in 2011, and median *BMI* for adults with CF increased from 21.2 to 22.1 kg/m^2 (normal range for healthy adults is 18.5–25) [35]. However, 2005 data from the CF Foundation Patient Registry Report (US) showed that nearly a quarter of children were below the 10th percentile weight-for-age and sex, and 22% of adults aged 18–30 years were underweight [29].

1.3.3. What are the causes of undernutrition?

Malnutrition in CF results from a combination of conditions—energy losses, high energy needs, and inadequate nutrient intake [18]. The primary cause of energy loss is malabsorption, often resulting from maldigestion due to insufficient release of pancreatic enzymes into the intestinal lumen (exocrine pancreatic insufficiency) [23]. Energy losses are further worsened when digestive abnormalities are associated with metabolic changes, e.g., intestinal inflammation, small intestinal bacterial overgrowth, low bicarbonate output, impaired insulin secretion with a variable degree of insulin resistance (CF-related diabetes) [36] and impaired liver function (CF-related liver disease) [37,38].

Furthermore, energy needs are higher in people with CF and pancreatic insufficiency in comparison with needs of healthy individuals, an observation supported by measurement of high resting energy expenditure in people with CF [39]. Such high energy expenditure correlates strongly with pancreatic insufficiency, although the mechanism remains unclear [18]. Further, high energy requirements have also been attributed to persistent lung inflammation and infections associated with CF [38,40,41].

People with CF, especially children and adolescents, are often unable to consume sufficient energy to overcome shortfalls due to inefficient energy use and increased energy needs. Psychosocial issues, such as stress and treatment noncompliance, may contribute to energy shortfalls [18]. Pulmonary inflammation, discomforts related to gastrointestinal problems (gastro-esophageal reflux, constipation, distal intestinal obstructive syndrome, bacterial overgrowth), and the side-effects of medications can also decrease appetite and interfere with intake goals [18,23,42].

1.3.4. What are the consequences of undernutrition?

Undernutrition affects respiratory muscle function, decreases exercise tolerance, and leads to immunological impairment [43]. While CF pathophysiology is directly linked to a deficit of energy intake relative to needs, CF also affects multiple body systems in ways that further worsen pulmonary status, impair growth, lower quality of life, and shorten life expectancy [44].

In infants and young children with CF, poor nutritional status results in stunted growth, as detected by low weight- and height-for-age percentiles [29,45,46]. If untreated, such CF-related undernutrition in infancy or early childhood can lead to the serious consequence of impaired cognitive function [47]. In cases of severe undernutrition in infants and children, lung function worsens markedly [46], and survival is poor [48].

As CF progresses in older children and in adults, a wide range of metabolic complications cause nutritional deficits, which further compromise quality of life [49] and increase mortality risk [50]. For example, CF-related diabetes—insulin deficiency and/or insulin resistance—causes and worsens malnutrition by lowering insulin's anabolic effects [51–53]. Similarly, CF-related liver disease and hepatic steatosis are associated with selective nutritional deficiencies, e.g., fat-soluble vitamins and EFA and calcium [37,54,55],

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Table 3
General guidelines for CF nutrition care.[a]

General guideline statements	Section
1. We recommend screening of all newborns for CF, and we recommend early initiation of nutritional management of those who are affected.	1
2. We recommend regular assessment of anthropometric parameters reflecting nutritional status, i.e., weight- and length-for-age percentiles for infants and children ≤2 years, weight-, length- and BMI- for-age percentiles for older children (>2years), and BMI for adults.	1
3. We suggest regular measurement of specific nutritional, functional, and disease-related markers as predictors of nutritional risk.	1
4. To prevent or delay onset of nutritional deficits, we recommend patient/parent education about nutrition; intake of energy that is age-appropriate and supports normal weight, with a wide interindividual range from about 1.1 to 2-times the reference intake for healthy populations. Advice on dietary intake of electrolytes, with supplementation as needed; supplementation of fat-soluble vitamins; and prescription of pancreatic enzyme replacement therapy (PERT) for individuals with pancreatic insufficiency.	2
5. We suggest advising patients on macronutrient balance in the diet, with attention to protein and fat intake that is sufficient to prevent or delay loss of muscle mass and function.	2
6. For effective management of undernutrition, we recommend specific criteria for action; how to assess and treat underlying causes; and ways to treat deficiencies.	3
We call for researchers to study new treatments for nutritional complications of cystic fibrosis—specific fatty acids, anti-osteoporotic agents, anti-inflammatory agents, anabolic therapies, or probiotics.	4

[a] For specific guidelines on nutrition care for individuals with cystic fibrosis, see the relevant manuscript section.

in turn worsening malnutrition and contributing to problems such as osteopenia and osteoporosis [56–58].

Taken together, such adverse consequences of nutrient deficits in infants, children, and adults with CF are a rationale for early and aggressive nutrition intervention, beginning in the first years of life and continuing over the lifespan [59,60].

1.4. General guidelines on nutrition care for cystic fibrosis

We emphasize six basic guidelines on screening, assessment, and interventions for nutrition care in individuals with cystic fibrosis (Table 3). While additional research trials will strengthen the evidence base for many recommendations, we specifically call for studies on new treatments for nutritional complications of specific fatty acids, anti-osteoporotic agents, anti-inflammatory agents, anabolic therapies, or probiotics.

2. A systematic approach to nutritional assessment and monitoring in CF

At all ages, individuals with CF are at nutritional risk; therefore, routine and complete nutritional assessments are essential to improve outcomes. For infants who are diagnosed by newborn screening, attention to nutrition is key to maintaining normal growth—even before signs of the CF phenotype become evident [59,61,62].

This section discusses specific assessment for markers of poor nutritional status (Table 4). As discussed previously, poor nutritional status has traditionally been defined by anthropometric cutoffs for weight- and length percentiles in infants and children up to 2 years [62,63], and by BMI cutoffs for children older than 2 years and for adults [29]. International growth and stature standards or references are available from the World Health Organization

Table 4
Specific guidelines for assessment and monitoring of nutritional status in patients with CF.

Specific guideline statements
We recommend measuring weight and length or height at each clinic visit. (Grade of evidence: **low**)
We recommend using these levels to indicate adequate nutritional status:
• Infants and children ≤2 years: 0 SD (50th percentile) of weight and length for a healthy same-age population.
Children 2–18 years: 0 SD (50th percentile) of BMI for a healthy, same-age population. Change in height percentile/SD score should be considered, as stunted children can have a normal BMI. Any height measurement should be interpreted taking parental height into consideration.
• Adults >18 years – BMI at or above 22 kg/m [2] for females and 23 kg/m [2] for males
(Grade of evidence: **low**)
For CF patients of all ages, we recommend routine and frequent monitoring of length/weight, weight- and length-for-age percentiles, or BMI.
For infants, we suggest clinic visits every 1–2 weeks until evidence of adequate nutrition and ideal nutritional status is established, then monthly through the first year of life and, if possible, through early childhood.
For older children and adults, we recommend monitoring growth (weight- and length-for-age percentiles) and BMI at least every 3 months. Malnourished and stunted patients should have more frequent monitoring than patients with good nutritional status.
(Grade of evidence: **low**)
We recommend assessment of bone mineral density by dual-energy X-ray absorptiometry (DXA), for all patients from 8 to 10 years of age. (Grade of evidence: **low**)
We suggest consideration of assessment of body composition in all patients using methods such as DXA, anthropometry, bioelectrical impedance, air displacement plethysmography, double labeled water measurement and hand grip strength
(Grade of evidence: **low**)
For pancreatic-sufficient infants, children, and adults, we suggest annual assessment of pancreatic function by fecal pancreatic elastase-1 determination, with the test repeated when inadequate growth and/or nutritional status occur(s).
For children, adolescents, and adults, we recommend assessing for pancreatic enzyme replacement therapy (PERT) need or adequacy of treatment by monitoring growth, nutritional status, and gastrointestinal symptoms; we suggest monitoring every month for children, every 3 months for adolescents, and every 6 months for adults. (Grade of evidence: **low**)
For children and adults, we suggest care managers consider annual nutritional review with blood tests (blood count, iron status, plasma fat-soluble vitamin levels, serum liver function tests, and electrolyte measurements). Plasma phospholipids or red blood cell fatty acids can be monitored if the assay is available. (Grade of evidence: **low**)
We recommend annual screening of all CF patients ≥ 10 years for glucose tolerance. (Grade of evidence: **low**)
We recommend regular assessment of pulmonary function (FEV_1); for the majority, every 3 months. (Grade of evidence: **low**)
We recommend that children and adolescents undergo dietary review (see section below) at least every 3 months, and adults undergo dietary review at least every 6 months, including questions about adherence to dietary advice. (Grade of evidence: **low**)
We recommend that calcium intake should be assessed at least annually. (Grade of evidence: **low**)
For women with CF who are or plan to become pregnant, we recommend increasing the frequency of monitoring and continuing after delivery. (Grade of evidence: **low**)

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Table 5
Assessment of nutritional status for people with CF.

Age	Assessment method and timing
Growth/Weight/Bone monitoring	
Overall	We recommend measuring weight and length/height at each clinic visit.
Infants and children <2 years of age; older children and adults	For infants, we recommend clinic visits every 1–2 weeks until evidence of adequate nutrition is established, then monthly through the first year of life, or longer if possible. We recommend monitoring older children and adults at least every 3 months.
All patients ≥8 years	We recommend assessment of bone mineral density using dual-energy X-ray absorptiometry (DXA), for all patients from 8 to 10 years of age every 1–5 years, depending on the age of the patient, value of the previous scan, and presence of risk factors. For patients younger than 20 years of age whose height is more than one standard deviation below age and sex matched healthy controls BMD Z score should be adjusted for height or statural age to avoid over estimating deficits in BMD in people with short stature [71]. We suggest consideration of assessment of body composition in all patients using methods such as DXA, anthropometry, bioelectrical impedance, air displacement plethysmography, double labeled water measurement and hand grip strength (Grade of evidence: **low**)
Nutrition monitoring	
Children and adults	We suggest care managers consider annual nutritional review with blood tests (blood count, iron status, plasma fat-soluble vitamin levels, plasma or serum phospholipid fatty acid patterns, serum liver function, and electrolyte measurements). Monitor pancreatic enzyme replacement therapy (PERT) and vitamin levels 3–6 months after initiation or change in dosage. We recommend care managers consider the following assessments, as they are markers of risk for malnutrition: • Measurement of pulmonary function (forced expiratory volume in 1 s, FEV_1) at least every 3 months for most patients • For pancreatic-sufficient children and adults, we suggest annual assessment of pancreatic function by fecal pancreatic elastase-1 determination, with the test repeated if growth and/or nutritional status is/are inadequate. • We recommend assessing for PERT need or adequacy of treatment by monitoring growth and/or nutritional status; we recommend monitoring every 3 months for adolescents, and every 6 months for adults. 72-hour fecal fat measurement and the calculation of the coefficient of fat absorption may be used in patients whose nutritional status is questionable. (Grade of evidence: **low**)
Dietary review	
Children and adults	We recommend that children undergo dietary review at least every 3 months, including questions about adherence to dietary advice. For adults, such reviews should be conducted at least every 6 months. (Grade of evidence: **low**)

(WHO) [64]. In addition, poor nutritional status is associated with evidence of poor pulmonary function and pancreatic insufficiency. Nutritional status can be assessed and monitored with serum markers and body composition.

2.1. Assessment of growth and BMI by age

For infants and children with CF, nutrition is considered adequate when growth is similar to that of an age-matched healthy population (Table 4). Ideally, growth charts should be appropriate to the nationality and ethnicity of the patient. If these are not available the world health organization growth charts should be used (www.who.int/childgrowth/standards/en/). For infants and young children, aim to achieve the 50th percentile of weight and length for a healthy same-age population up to age two years. For older children and adolescents 2–18 years, the target is a body mass index (BMI) at or above the 50th percentile for healthy children. For CF adults over the age of 18 years, the target is a BMI at or above 22 kg/m [2] for females and 23 kg/m [2] for males [32].

2.2. Assessment of nutritional status and nutrition-related functions

This section presents guidelines for monitoring and timing to assess nutritional status (Table 5).

2.2.1. Serum markers of nutrition

Biochemical markers of nutrition status or risk factors include blood count, iron status, plasma fat-soluble vitamin levels, serum liver function tests, and electrolyte measurements [9,11,65–67]. Plasma phospholipids or red blood cell fatty acids can be monitored if the assay if available [32,65].

2.2.2. Body composition

Body composition can be assessed by a number of different techniques. These include dual-energy X-ray absorptiometry (DXA), anthropometry, bioelectrical impedance, air displacement plethysmography, double labeled water measurement and hand grip strength. However not all of these have been validated in CF. Lean body mass (LBM) and bone mineral content (BMC) are more sensitive indicators of nutritional deficit than low BMI; low values predict impaired lung function in children [68] and in adults with CF [68,69]. The European Cystic Fibrosis Bone Mineralisation Guidelines recommend that DXA is used to assess bone mineral density in all patients from the age of 8–10 years of age [71]. This measurement should be repeated every 1–5 years, depending on the age of the patient, value of the previous scan, and presence of risk factors (e.g., physical inactivity, glucocorticoid therapy) [70,71]. For patients younger than 20 years of age whose height is more than one standard deviation below age and sex matched healthy controls, BMD Z score should be adjusted for height or statural age to avoid over estimating deficits in BMD in people with short stature [71].

2.2.3. Electrolytes

Monitor the status of sodium, as discussed in section 2c.

2.2.4. Dietary review

A dietary review is appropriate for patients at nutritional risk, especially children who are consuming or skipping meals and snacks during school. A 24-h recall is a useful qualitative tool, but a longer 3–5 day diet record is necessary for a quantitative evaluation of energy and nutrient intake [9]. Because of the importance of adequate and appropriate dietary intake, we suggest that young children and adolescents undergo dietary review at least every 3 months [9,11] and adults at least every 6 months, including questions about adherence to dietary advice.

2.2.5. Pulmonary function

Pulmonary function is assessed as % predicted forced expiratory volume in 1 s (FEV_1); normal ranges of weight-for-age/length-for-age in children < 2 years old or optimal BMI in older children and

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adults correlate with better FEV_1 status [29]. As such, nutritional intervention for weight gain and growth improvement is expected to improve FEV_1 in individuals who are underweight or small-for-age; direct studies are needed. We recommend pulmonary function testing at least every 3 months [32,44].

2.2.6. Pancreatic function

Inadequate function of the pancreas contributes to malnutrition in CF patients. Evidence of pancreatic insufficiency (PI), i.e. a deficit of digestive enzymes, underlies inadequate energy absorption by infants, children, or adults. PI occurs when postprandial enzyme output is $\leq$10% of normal [72]. PERT is used to treat PI in infants, children, and adults [29,62,63]. Dosages are determined primarily by lipid content of the diet and amount of lipase needed.

PI is diagnosed by low levels of measured fecal pancreatic elastase-1 (<100 μg/g stool) and occurs in 85–90% of patients [38]. PI often evolves in the first year of life [62], and is a major reason for failure-to-thrive in infancy, when up to 80% of fat is excreted in stools because of lipase deficiency [38]. Pancreatic enzyme function can be better estimated by a fat balance study with assessment of dietary fat intake and fat excretion over 3 days [11] and determination of the coefficient of fat absorption.

Some CF patients who are initially pancreatic-sufficient (PS) later become PI as CF disease causes progressive pancreatic damage. For pancreatic sufficient infants and children, we recommend annual assessment of pancreatic function by fecal pancreatic elastase-1 determination, with the test repeated if growth is inadequate [62,63]. We recommend monitoring growth and/or nutritional status at regular intervals to determine the need for PERT or adequacy of treatment [32] – at every clinic visit for infants, every 3 months for older children and adolescents, and every 6 months for adults.

2.2.7. Liver function

Significant liver disease occurs in 10% of CF patients. Malnutrition is a common problem in people with CF liver disease. Nutritional support is therefore an integral part of the management of liver disease. It is important to monitor liver function as a part of disease management [73]. CF-related liver disease should be considered if at least 2 of the following variables are present: abnormal physical examination (hepatomegaly), persistently abnormal liver function test results and or pathological ultrasonography. If there is diagnostic doubt, a liver biopsy may be indicated [37]. Debray et al. defined abnormal liver function as increases in transaminases (aspartate transaminase and alanine transaminase) and gamma-glutamyl transpeptidase levels above the upper normal limits in at least 3 consecutive determinations over 12 months after excluding other causes of liver disease [37].

In order to detect pre-symptomatic signs, we suggest care managers consider annual screening for liver disease with physical examination for signs, enzyme assays, and ultrasound [37]. If early signs of liver disease are detected, refer to best practice guidelines for management of liver disease [37].

2.2.8. Nutrition monitoring in pregnancy

We recommend increasing the frequency of monitoring in patients planning a pregnancy and in pregnant patients [16,74], and we recommend close follow-up after delivery. Breastfeeding increases nutritional demands on the lactating mother and may need to be discontinued in women with a marginal nutritional status or malnutrition [16].

3. Preventing undernutrition: feeding people with CF

The association between good nutritional status and favorable CF outcomes inspires clinicians to be attentive to the nutritional care as a mainstay of CF treatment. This association also motivates parents and patients to adhere to nutrition recommendations, i.e., balanced and high-energy intake and appropriate PERT.

3.1. Feeding the newly diagnosed infant

It is important to identify CF in the first days of life with newborn screening so that medical and nutritional intervention can start immediately, in order to reduce the risk of failure to attain normal growth. While infants with CF may appear well, subtle early changes require careful monitoring and timely intervention to manage properly [62,63]. Currently, there is a lack of high quality evidence to support nutritional recommendations for infants newly diagnosed with CF [75]. For that reason, it is appropriate that infants identified with CF be given the opportunity to participate in randomized controlled trials to increase the evidence base for the most adequate nutritional management of infants with CF.

We recommend exclusive breastfeeding for newly diagnosed infants with CF [62,63]. A retrospective analysis of infants with CF found that those who were breastfed had better lung function and fewer infections that those who were not [76]. The authors suggested that this may be due to improved immune function and direct delivery of docosahexanoic acid (DHA) to the infant. When breastfeeding is not possible, we recommend the use of a regular infant formula. There is no evidence to support the routine use of a high energy or hydrolyzed formula, though they may be of value in some infants e.g. those with poor growth or with malabsorption that is not related to CF [63]. Additional sodium supplementation may be required in both formula or breastfed infants (see below).

Solids should be introduced at the same age as recommended for the non CF population. We recommend nutrition counseling for all families of infants with CF to teach appropriate feeding strategies, as part of multidisciplinary care for newly diagnosed infants [63].

Guidelines: Feeding infants newly diagnosed with CF

- We recommend newborn screening and early management of CF to reduce the risk of malnutrition. (Grade of evidence: **low**)
- We recommend exclusive breastfeeding for newly diagnosed infants with CF, and we recommend a regular infant formula if breastfeeding is not possible. (Grade of evidence: **low**)
- We recommend nutrition education and behavioral counseling for all families of infants with CF. (Grade of evidence: **high**)

3.2. Feeding children and adults

3.2.1. Nutrition counseling

Dietary counseling is essential throughout early childhood when long-term feeding habits are being established [32]. Advice from a CF dietitian should be tailored to the individuals' age and evolving independence, clinical status, and support the goal of self-care [77]. All young children are sometimes reluctant to try new foods, and have negative interactions with their parents during mealtimes. Left uncorrected, feeding problems may develop, which can jeopardize the child's caloric intake [78–81]. Therefore, we also recommend behavioral counseling to achieve and maintain healthy feeding and eating behaviors in at-risk children. Disturbed eating behavior has also been documented in adults and this may also need addressing (for references, see the “Behavioral intervention” section in the “Feeding undernourished

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patients with CF" chapter).

Guideline: Nutrition counseling

We recommend nutrition education and behavioral counseling for patients with CF and their families to achieve and maintain healthy feeding/eating behaviors. (Grade of evidence: **high**)

3.2.2. Energy and macronutrients

Nutritional guidelines for children and adults with CF have traditionally focused on meeting body weight or BMI targets by increasing fat intake to achieve energy balance and improve survival [18,29]. Loss of lean body mass is reported in adolescents and adults with CF [24], and EFA abnormalities are common in infants and children with CF [11]. As nutritional care advances to reflect new knowledge, it is important to consider dietary recommendations for protein intake and fatty acid supplementation.

3.2.3. Energy targets

People with CF may need higher energy intake than the general population to achieve normal growth in children and adequate nutritional status in adults. European guidelines recommend that energy intake for people with CF range from 120 to 150% of energy needs for the healthy population of similar age, sex, and size [11]. US recommendations cite similarly high energy intakes (110%–200% of energy needs for the healthy population) for increasing weight [29]. A normal nutritional status may warrant intakes closer to normal. Indeed energy needs vary greatly between individuals depending on degree of malabsorption, lung function, level of chronic inflammation, and presence of acute respiratory exacerbations [11].

In people with CF, compensatory mechanisms appear to play roles in releasing energy from food sources, e.g., food breakdown by salivary amylase, gastric lipase and pepsin, and by colonic microbiota [23]. Such mechanisms are less efficient than usual digestive pathways, necessitating higher dietary intake.

Guidelines: Energy intake
(Table 6)

- We suggest adjusting energy intake upward to achieve normal growth and nutritional status while avoiding obesity
- We recommend energy intake targets by age
- We recommend consideration of macronutrient balance goals, especially protein and fat.

(Grade of evidence: **high** for increased energy intake; **low** for macronutrient balance)

3.3. Specific macronutrient targets

3.3.1. Balancing protein and fat intake

The European Food Safety Authority (EFSA) recommends a population reference intake (PRI) of 0.83 g of protein/kg body weight per day in adults [82]. Protein needs are likely to be higher for individuals with CF compared to non-CF individuals, i.e., 20% or more of macronutrient intake, consistent with protein intake needs for individuals with other inflammatory diseases [24]. Current consensus guidelines recommend that children with CF consume 35–40% of their caloric intake from fat, 20% from protein and 40–45% from carbohydrates [24,27,83]. Adequate supplies of energy are essential to spare protein breakdown and compensate for high linoleic acid turnover [26].

The long-term health effects of overweight and obesity suggest that balanced intake of protein and fat should be maintained when overall energy intake is increased. Researchers suggest that some saturated fats in the diet may have potential to increase long term risk for cardiovascular disease [17,84]. Furthermore, high fat mass but low lean body mass (muscle) does not necessarily correlate with better lung function, and in fact predicts poor CF disease prognosis [24].

We cannot presently make evidence-based recommendations for daily protein intake of patients with CF [24,29]; further studies are needed to develop such guidelines for protein thresholds in children and adults. Engelen and colleagues advise that determining the optimal protein needs depends on each individual's condition [24].

3.4. Minerals, trace elements, and vitamins

3.4.1. Electrolytes, minerals and trace elements

Patients with CF may have higher than normal requirements for salt, calcium, iron, zinc, and selenium as a consequence of the increased sweating, intestinal malabsorption, and chronic inflammation that are common in CF.

3.4.1.1. Sodium. Excessive salt loss in sweat can result in inadequate levels of sodium in people with CF of all ages [85].

There is risk for sodium loss in hot environmental conditions, body fever, rapid breathing, and fluid loss due to diarrhea, vomiting, or stoma output [25,63]. Sodium deficiency can be a particular problem for infants, as it can lead to impaired growth [62,63,86,87]. Furthermore, the sodium content of breast milk and standard infant formula is relatively low (<7 mmol/L in breast milk, and <15 mmol/L in formula) [87,88]; most first baby foods also have low sodium content [62].

3.4.1.2. Infants. The 2002 European and UK consensus guidelines for the management of CF patients note infants may be at a particular need for sodium supplementation, but the guidelines do not recommend routine supplementation [10,11]. The North American evidence-based guidelines for the management of infants with CF recommend routine sodium supplementation for all infants with CF, to a maximum of 4 mmol/kg body weight/day [62].

These guidelines recommend assessing infants' needs for sodium supplementation on an individual basis, taking climate and sodium losses into consideration. In most cases, supplementation with 1–2 mmol/kg body weight/day of sodium should correct deficiency [63] although more may be required, with or without

Table 6
Energy intake for people with CF: consensus guidelines.

Age	Energy target	Detail
Infants and children ≤2 years	110%–200% of energy requirements for same-age healthy infants and children	Energy intake should be adapted to achieve normal weight- and length-for-age percentiles [29,63,82].
Children 2–18 years	110%–200% of energy requirements for same-age healthy children	Energy intake should be adapted to achieve target BMI percentile tailored to one-year age intervals [27,29,82].
Adults >18 years	110%–200% of energy requirements for same-age healthy population to maintain BMI targets	Energy intake should be adapted to achieve BMI targets [29,82].

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Table 7
Sodium supplementation (as sodium chloride) for people with CF: consensus recommendations. (Grade of evidence: **moderate**).

Age	Sodium supplementation[a]	Detail
Breastfed infants 0–6 months	1–2 mmol per kg/day	For infants at risk of sodium deficiency give salt in small portions throughout the day, diluted in water or fruit juice.
For infants with special considerations (see detail, right)	Up to 4 mmol per kg/day	Increase intake for infants living in hot ambient temperatures; or for those with increased fluid loss due to vomiting, fever, diarrhea, or tachypnea; or infants with ostomies.
Older children through adults	Salty foods or sodium chloride capsules or vials	Supplement in stress situations when excessive sweating is expected (i.e., fever, exercise/sports, hot weather).

[a] To convert mmol to mg of sodium, chloride, or sodium chloride, multiply mmol by 23, 35, or 58 (the molecular weights of sodium, chloride, and sodium chloride), respectively.

hot weather [25,86]. Salt (sodium chloride) should be given in small portions throughout the day, diluted in water or formula.

3.4.1.3. Older children and adults. While a Western diet with processed foods provides adequate sodium for most older children and adults [89], fever, exercise, or hot weather can lead to deficits.

We suggest the need for sodium supplementation can be assessed by measuring fractional excretion of sodium (FENa); maintain a FENa level between 0.5% and 1.5%. For routine practice, a urinary sodium: creatinine ratio is easier to measure and correlates with FENa (corresponding range 17–52 mmol/mmol) [86]. If supplementation is necessary, sodium chloride capsules (or sodium chloride doses distributed in vials) can be administered several times a day.

Guidelines: Salt

Supplementation:

We recommend specific levels of salt supplementation depending on age and situation (Table 7). To convert mmol to mg of sodium, chloride, or sodium chloride, multiply mmol by 23, 35, or 58 (the molecular weights of sodium, chloride, and sodium chloride), respectively. In ¼ teaspoon salt, about 25 mmol or 575 mg of sodium is delivered.

Monitoring:
We suggest that the need for salt/sodium supplementation can be assessed by measuring fractional excretion of sodium (FENa) and maintaining a FENa level between 0.5% and 1.5%. For routine practice, a urinary sodium: creatinine ratio is easier to measure and correlates with FENa (corresponding range 17–52 mmol/mmol).

3.4.2. Calcium

Calcium, important for bone health, can be in short supply in people with CF due to deficiency of vitamin D (a fat-soluble vitamin) and low intake of dietary calcium [90]. Other contributors to negative calcium imbalance include gastrointestinal malabsorption that may not be fully corrected [70] by PERT and increased endogenous fecal calcium loss [91].

Calcium intake should be assessed at least annually [71], and more frequently in children with abnormal growth rate, weight stagnation, or weight loss. Currently, no simple test of calcium status is available in clinical practice [71]. Daily calcium intakes should at a minimum achieve dietary intake recommended by the European Food Safety Authority (Table 8) [92].

Those with suboptimal calcium intakes should increase dietary intake of calcium, mainly dairy products such as cheese [90,93]. If necessary, calcium supplements can be given [71,93]. It is important to provide enough PERT to maintain lipolysis so calcium will not be excreted in soaps.

Guidelines: Calcium

Supplementation:
- We recommend that daily calcium intake should normal dietary reference values for same age healthy people. (Grade of evidence: **low**)
- We recommend that individuals with suboptimal calcium intakes should increase dietary intake of calcium-rich foods, mainly dairy products, and should take calcium supplements if dietary intake remains low. (Grade of evidence: **low**)
- **Monitoring:**

We recommend calcium intake should be assessed at least annually. (Grade of evidence: **low**)

3.4.3. Iron

Iron deficiency is common in people with CF, ranging from 11% of children [94], to over half of stable adults with CF [95]. CF patients with plasma iron deficiency tend to have iron deficiency anemia, poor lung function and overall health [95], and children may have poor appetite [9]. Multiple factors can contribute to iron deficiency, including malabsorption, chronic infection and inflammation, chronic blood loss, and inadequate intake [96]. Monitoring iron levels is complicated by infection, which influences serum ferritin and transferrin; serum transferrin receptors (sTfR) are not affected by inflammation, and are thus a more accurate measure of iron level, but a test for sTfR is not widely available [9,97,98]. For CF patients with iron deficiency, we suggest resolving underlying inflammation [99], and supplementing with iron only if the deficiency persists.

We suggest monitoring child, adolescent, and adult patients annually [9] for anemia by first determining serum iron values. If serum iron values are low, it is necessary to use another measure to differentiate between iron deficiency anemia (IDA) and anemia of chronic inflammation (ACI). As shown (Table 9), levels of serum ferritin, total iron binding capacity (TIBC), or transferrin saturation can facilitate differentiation between anemia due to iron deficiency versus anemia resulting from chronic inflammation [96,100]. When

Table 8
Calcium intake for people with CF: recommendations guided by EFSA [92].

Age	Dietary reference values [92]
0–6 months	200 mg
7–11 months	280 mg
1–3 years	450 mg
4–10 years	800 mg
11–17 years	1150 mg
18–25 years	1000 mg
>25 years	950 mg

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Table 9
Use an additional measure of iron deficiency to differentiate between forms of anemia.

Use normal reference range[a] for:	Iron deficiency anemia	Anemia of chronic inflammation	Both forms of anemia
Serum iron	Below normal	Below normal	Below normal
Serum ferritin	Below normal	Above normal	Varies
Total iron binding capacity	Above normal	Below or normal[b]	Varies
Transferrin saturation, percent	Below normal	Below normal	Below normal

[a] Use normal reference range provided by the laboratory processing the sample.
[b] Either below the normal reference range or within the normal reference range.

IDA and ACI are both present, serum ferritin and TIBC may be increased, decreased, or within the normal range, due to offsetting influences of the two conditions.

Guidelines: Iron

- **Supplementation:**
In cases of iron deficiency, we recommend resolving underlying inflammation, and supplementing with iron only if deficiency persists. (Grade of evidence: **moderate**)
- **Monitoring:**
We suggest monitoring children, adolescent, and adult patients annually using serum iron determination, differentiating between iron deficiency anemia and anemia of chronic inflammation; if iron deficiency is suspected, increase frequency of monitoring. (Grade of evidence: **low**)

3.4.4. Zinc

Zinc status in people with CF has been variously reported as adequate and low, depending on the study [101–103]. This may be a result of measuring plasma zinc levels, the method used in most studies, which is not a sensitive marker of zinc status and is highly variable under different conditions. Use of PERT can improve zinc absorption [11]. Zinc deficiency can be associated with a broad range of symptoms in CF, including growth retardation, increased susceptibility to infections, delayed sexual maturation, eye problems, and anorexia caused by reduced sense of taste (hypogeusia) [104].

We suggest zinc supplementation for people with CF who are at risk of zinc insufficiency (Table 10).

Zinc insufficiency may be evidenced by insufficient growth in infants or children with CF, and vitamin A deficiency or steatorrhea in people of any age who have CF [11,62]. Like all mineral supplements, zinc is best tolerated in divided doses [62].

Guideline: Zinc

Supplementation:
- We suggest zinc supplementation for people with CF who are at risk of zinc insufficiency (e.g., growth retardation, increased susceptibility to infections, delayed sexual maturation, eye problems, and anorexia). (Grade of evidence: **low**)

3.4.5. Glutathione

There are no data supporting the use of glutathione therapy in CF patients [105].

3.4.6. Selenium

Dietary selenium is important as an essential constituent in the antioxidant glutathione peroxidase [106], and plays an important role in immune responses. Though selenium status has been reported to be low in some people with CF, this element has a narrow therapeutic range and fatalities have been reported with inorganic selenium supplementation in people with CF [38]. At the same time, some pancreatic enzyme replacement preparations contain selenium in adequate and safe amounts [107]. We do not suggest routine supplementation of selenium [62] outside of very limited geographical areas where low serum selenium can result from low selenium content in soil and agricultural products [11,108].

Guideline: Selenium

- **Supplementation:**
We do not recommend routine use of selenium supplements for people with CF. (Grade of evidence: **low**)

3.5. Fat-soluble vitamins (Table 11)

The disturbed mechanism of fat absorption resulting from pancreatic insufficiency can cause people with CF to become deficient in fat-soluble vitamins, particularly vitamins A, E, and K. Without adequate sun exposure, these individuals can also become vitamin D deficient [38]. Even people with CF who are pancreatic sufficient have been shown to be at risk for deficiencies of fat-soluble vitamins [109].

Fat-soluble vitamin deficiency is common, occurring in 10–35% of children with pancreatic insufficiency [110]. It is unusual, however, for people with CF to show clinical signs of overt deficiency. Instead, the goal of evaluation and treatment is to correct suboptimal levels and achieve optimal biochemical values of these vitamins [111]. Plasma levels of fat-soluble vitamins should be measured at least annually in all people with CF [11].

For pancreatic insufficient patients, we recommend evaluating plasma levels of fat-soluble vitamins after initiation of enzyme and

Table 10
Zinc supplementation for people with CF: consensus guidelines.

Age	Recommended supplementation	Recommended dosing period
Infants and children <2 years and at risk of zinc insufficiency	1 mg/kg/day (max 15 mg/day)	6 months
Children 2–18 years and at risk of zinc insufficiency	15 mg/day	6 months
Adults >18 years and at risk of zinc insufficiency	25 mg/day	6 months

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vitamin supplementation; 3–6 months after initiation or change in vitamin therapy; and annually thereafter [11,65,112]. Vitamin supplements should be taken together with high fat food and pancreatic enzyme supplements to improve absorption. When biochemical deficiency is detected despite adequate vitamin supplementation, poor adherence or poor absorption of supplements must be ruled out before adjusting the dosage. For pancreatic sufficient patients, we recommend assessing vitamin sufficiency annually using plasma levels.

3.5.1. Vitamin A

Vitamin A deficiency in CF is common, and has been reported in 10%–40% of patients with CF [113,114]. It can occur independent of age, nutritional status, meconium ileus, disease severity, genotype, and exocrine pancreatic function [115]. For people with CF, low vitamin A levels are associated with poorer clinical status, impaired lung function, and increased pulmonary exacerbations [116]. Symptoms of clinical deficiency are extremely rare. Reports include benign intracranial hypertension (pseudotumor cerebri) or uni- or bilateral facial palsy in an infant [117], and xeropthalmia, which can progress to conjunctival dryness, and ultimately corneal ulceration and blindness [118].

Low plasma vitamin A levels can occur in pancreatic insufficient patients on PERT and in pancreatic sufficient patients [115]. This deficit may be a consequence of disturbed mobilization of hepatic stores due to reduced levels of retinol binding protein (RBP) [119] that can occur in advanced liver disease, malnutrition, or zinc deficiency [118]. When severe liver disease is present and retinol binding protein (RBP) is low, supplementation should be reduced to avoid dangerous hypervitaminosis [120].

We recommend vitamin A supplementation that aims to achieve the normal range of serum retinol concentrations for healthy people; the normal range is advised by the laboratory performing the assay [114]. Using retinol, start with a low dose; increase dose as guided by serum values. Beta carotene is a precursor to vitamin A, and in contrast to preformed retinol, is subject to negative feedback control and therefore may be safer to use [111,121]. Alternatively, a daily provitamin beta carotene dose of 1 mg/kg body weight/day for 12 weeks, followed by a maintenance dose (maximum of 10 mg/day) was found to be efficacious and safe for children aged 6–18 years [122].

We recommend monitoring serum levels to guide initial and continuing vitamin A supplement doses [9,11]. Once normal vitamin A levels are achieved, we recommend annual serum monitoring [9,11]. Serum vitamin A levels do not correlate well with tissue concentrations of vitamin A, and should not be assessed during the acute phase of infection when serum retinol concentrations fall in response to inflammation [45,123].

High retinol serum concentrations indicate a risk for toxicity, which can lead to liver fibrosis, lower bone mineral density and increased risk of fractures [114]. Studies show that a majority of people with CF who were clinically stable exceeded the recommended upper limit of intake for vitamin A from supplements and their regular diet; and supplementary vitamin A was unnecessary in 20–25% of them [114,124].

The potential toxicity of vitamin A is a concern. It is important to factor in dietary intake when determining supplement dosing to avoid harmful vitamin A toxicity [111,114,124]. In addition, the risk of hypervitaminosis A is higher with water-miscible and water-soluble forms than with oil-based supplements [125].

An adequate supply of vitamin A is important prior to and during pregnancy, but special consideration should be given to the dose, since both hyper- and hypovitaminosis A can cause harm to the mother and her fetus [126,127]. We suggest assessing vitamin A intake and blood levels before conception or early in pregnancy, and keeping intakes below 10,000 IU/day [16]. If plasma levels are low, consider both the benefits and risks of supplementation to both mother and fetus.

Table 11
Fat-soluble vitamin guidelines for pancreatic insufficient patients with CF: consensus guidelines.

Vitamin	Supplementation	Serum reference values and monitoring frequency
Fat-soluble vitamins		
Vitamin A	Amounts dependent on serum values, and supplement form:	Normal reference range provided by the laboratory processing the sample
	Retinol (preformed):	
	• Start low	Monitor annually and 3–6 months after a dosage change.
	• Adapt rapidly to target normal serum reference range	Also test when pregnancy is considered.
	Beta carotene (provitamin A):	
	• Prescribe 1 mg/kg/day (maximum 50 mg/day) for 12 weeks	
	• Follow with maintenance dose (maximum 10 mg/day)	
Vitamin D	Dependent on serum values, which vary with dietary intake and sun exposure:	Serum-25 (OH) D minimum 20 ng/mL (50 nmol/L)
	• Starting dose of D3 (cholecalciferol) -Infants 400 IU/day (advance to upper limit of 1000 IU/day) -All others 800 IU/day (advance to upper limit of 2000 for children 1–10 years, and 4000 IU/day for older)	Monitor annually, and check 3–6 months after a dosage change
	• Maintenance dose: adapt to annual serum values, preferably measured at the end of dark months	
Vitamin E (tocopherols)	α-tocopherol dosing: 100–400 IU/day 50 IU/day for infants < 12 months (1 mg = 1.49 IU)	Plasma α-tocopherol:cholesterol ratio > 5.4 mg/g Monitor annually, and check 3–6 months after a dosage change
Vitamin K	Vitamin K_1 • Infants: 0.3–1.0 mg/day • Older children and adults: 1–10 mg/day	Routine biochemical measurement not widely available
Water-soluble vitamins		
Folic acid	Women planning to become pregnant, and during first trimester of pregnancy: 400 μg/day	
Vitamin B_{12}	May need supplementation after extensive ileal resection. When deficient: 100 μg/month, intramuscular injection	
Vitamin C	Supplement only when nutritional intake is insufficient	

Abbreviation: 25(OH)D = 25-hydroxyvitamin D.

Guidelines: Vitamin A

- **Supplementation:**
  - We suggest vitamin A supplementation that aims to achieve the normal range of serum retinol concentrations for healthy, same-age individuals.
  - We recommend assessment of vitamin A intake and blood levels in women before conception or early in pregnancy. We suggest consideration of the benefits and risks of supplementation to both mother and child if plasma levels are low, and keeping vitamin A intakes in these women below 10,000 IU/day.
- **Monitoring:**
  - We recommend serum monitoring of vitamin A annually, 3–6 months after a dosage change and when pregnancy is considered.

(Grade of evidence: **low**)

3.5.2. Vitamin D

Vitamin D plays a major role in intestinal calcium absorption, and deficiency of this vitamin is one of several factors that can contribute to reduced bone mineral density in people with CF [128]. Vitamin D deficiency is common and has been reported in 22% of infants with CF at newborn screening [113]; and more than 90% of older children and young adults with CF were found to have sub-optimal levels of 25-hydroxy vitamin D (25(OH)D) [129].

The major source of vitamin D, exposure of skin to sunlight, can vary widely between individuals and available sunlight, which in turn depends on geographical latitude [130]. The best indicator of vitamin D status is serum 25(OH)D [131].

There is lack of consensus on optimal serum concentrations of vitamin D. A recent review found that people with CF who receive vitamin D supplements have significantly higher 25(OH)D levels, but found no evidence of clinical benefit or harm [5]. The US Cystic Fibrosis Foundation recommends levels above 30 ng/mL (75 nmol/L), assuming this level offers extra skeletal health benefit [128]. The European Cystic Fibrosis Bone Mineralization Guidelines recommend a minimum serum 25(OH)D threshold of 20 ng/mL (50 nmol/L) [71].

We suggest supplementation of vitamin D for people with CF to maintain serum 25(OH) concentration above 20 ng/mL (50 nmol/L) [132–134]. The supplemental dose should take into consideration dietary intake and sunlight exposure of the individual patient [130]. We recommend that pregnant women take additional vitamin D supplement of 600 IU (15 mcg) per day [134]. Our recommendations are consistent with European recommendations on Tolerable Upper Limits and with other cystic fibrosis nutrition guidelines [131,132]. While there is some debate, vitamins D_3 is preferred over D_2 for supplementation in people with CF [131,135]. We recommend serum monitoring of 25(OH)D annually [25], preferably at the end of dark months, as well as 3–6 months after a dosage change [131].

Guidelines: Vitamin D

- **Supplementation**
  - We suggest supplementation of vitamin D as needed to maintain 25-hydroxy vitamin D (25(OH)D) concentration above 20 ng/mL (50 nmol/L).
  - We suggest safe sunlight exposure.
  - We suggest pregnant women take additional vitamin D supplement of 600 IU/day (15 mcg/day).
- **Monitoring:**
  - We recommend serum monitoring of 25(OH)D at least annually (preferably at the end of darker months) and 3–6 months after a dosage change.

(Grade of evidence: **low**)

There is ongoing debate about the optimal dosing regime and most efficacious formula for vitamin D supplementation [136]. Recent research considered an alternative method for dosing vitamin D supplements. Shepherd and colleagues demonstrated that a single high oral dose of cholecalciferol (vitamin D_3), known as “Stosstherapie” (from the German word for “push therapy”), in conjunction with maintenance vitamin D therapy, can safely elevate and maintain an elevated 25(OH)D level above 75 nmol/L over a 12 month period in children with CF [136].

A recent review considered the chronic suboptimal vitamin D levels in many people with CF despite supplementation regimens. The authors hypothesized that the bioavailability of vitamin D is impaired in these patients due to mechanisms beyond the current understanding of maldigestion and malabsorption of fat. The authors suggested that vitamin D status may influence the strength of respiratory muscles; lung structure and function; infection-fighting capability; and insulin secretion [137].

3.5.3. Vitamin E

Alpha-tocopherol (α-tocopherol), the major compound of vitamin E, is the primary scavenger of free oxygen radicals, and thus helps protect fatty acids from oxidative damage and preserve cellular membranes. Clinical deficiency of vitamin E can lead to serious consequences such as hemolytic anemia, neuromuscular degeneration, and retinal and cognitive deficits [11]. Biochemical deficiencies of vitamin E are common—up to 23% in newly diagnosed infants [113,115], and 14% in older children [110], leaving plasma lipids in these patients vulnerable to oxidative damage [11]. An individual's requirements for vitamin E increase with oxidative stress during pulmonary exacerbations of CF and with aging [138]. Chronic respiratory infection and inflammation increase oxidative stress, which further suppresses CFTR function [139], making adequate supplies of vitamin E even more important.

Four studies of vitamin E supplementation in people with CF show supplementation can increase serum vitamin E levels, but direct evidence demonstrating clinical benefit is not currently available [123]. The risks and benefits of long-term exposure to high serum levels of vitamin E in this population should also be investigated [140]. We suggest regular supplementation of vitamin E (α-tocopherol) for people with CF to maintain serum α-tocopherol levels in the normal range [11]. Because bile acids are essential for absorption of vitamin E, patients with cholestasis will need to use a water-soluble preparation [141].

Traditionally, serum levels less than 300 μg/dL indicated deficiency [113]. Since vitamin E levels follow those of lipids, determination of the plasma α-tocopherol:total lipid ratio has been advised as an index of true vitamin E status [11]. This approach helps overcome the concern that some physiological conditions can lead to an appearance of high or low vitamin E levels. Vitamin E levels may seem low because of hypolipidemia. On the other hand, vitamin E levels may appear high as CF survival increases and elevation of certain lipids become more common in older surviving patients [33,142]. In such situations, it may be more accurate to use α-tocopherol:total lipid ratio (in fasting samples), or α-tocopherol:cholesterol or α-tocopherol:polyunsaturated fatty acids ratios (in non-fasting samples). While a serum α-tocopherol:cholesterol ratio of 2.47 mg/g is accepted as the lower limit of normal in healthy people, a higher cutoff ratio of 5.4 mg/g is suggested in CF [140]. We suggest that vitamin E levels be assessed at least annually in all people with CF [9,11], and 3–6 months after a dosage change [143]. Nevertheless, debate continues about whether to use plasma/serum α-tocopherol levels or serum α-

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tocopherol:cholesterol ratio as a biomarker for assessment of vitamin E status.

Guidelines: Vitamin E

- **Supplementation:**
We suggest regular supplementation of vitamin E to maintain serum α-tocopherol:cholesterol ratio above 5.4 mg/g.
- **Monitoring:**
We suggest serum monitoring at least annually and 3–6 months after a dosage change.

(Grade of evidence: **low**)

3.5.4. Vitamin K

Vitamin K status is often suboptimal in people with CF, and appears to be deficient in all patients with CF-related liver disease [110,144,145]. Vitamin K plays a role in blood clotting and bone health [108], and deficiency can result in clinically significant bleeding (e.g., intracranial hemorrhage in infants), and may contribute to low bone mineral density [71,146]. Vitamin K deficiency has been attributed to fat malabsorption, long-term antibiotic use, and liver disease [145]. All exclusively breastfed infants with CF (like their healthy peers) should receive vitamin K supplementation.

There are no routinely used biochemical indicators of vitamin K status. It can be evaluated by measuring serum concentrations of vitamin K, PIVKA-II (protein induced by vitamin K absence) and undercarboxylated osteocalcin, but these markers are not usually measured in routine clinical practice due to cost. Prothrombin time can be measured but is insensitive, only becoming elevated in severe deficiency [71].

Vitamin K1 (phytomenadione, phylloquinone), the form of vitamin K present in green leafy vegetables and vegetable oils, is recommended as the safest form of supplementation, and preferred over menadione salts. In a small but well-performed study, a daily dose of 5 mg vitamin K_1 was shown to increase the serum level of vitamin K_1 in children with CF [147].

There is insufficient evidence to determine the most effective dosing for vitamin K_1 supplements [71]. At this time, we suggest regular supplementation of vitamin K_1 at 0.3–1.0 mg/day for infants [71]. For older children and adults, we suggest 1–10 mg/day of vitamin K_1 depending on age (Table 11) [71,144]. Higher doses may be considered for those with low vitamin K levels or with higher risk, for example due to long term antibiotic use [148]. Daily administration is preferred because of the low storage capacity of vitamin K [147,148].

Special attention should be paid to CF newborns, exclusively breastfed CF infants, and people with CF receiving broad spectrum antibiotic treatment, those with liver disease, or severe malabsorption [11]. Vitamin K toxicity (phylloquinone) is not a concern, as there are no known adverse effects of supplementation [108].

Guidelines: Vitamin K_1

- **Supplementation:**
We suggest regular supplementation of vitamin K_1 in doses according to age or risk: for infants, 0.3–1 mg/day; for older children and adults, 1–10 mg/day. (Grade of evidence: **low**)

3.6. Water-soluble vitamins (Table 11)

Deficiency of water-soluble vitamins (folic acid, vitamin B_{12}, and vitamin C) is rare in uncomplicated CF. However, for all women planning to become pregnant, we recommend a daily supplement of 400 mcg of folic acid in the preconceptional period and throughout the first trimester to prevent neural tube defects [16]. Deficiency of vitamin B_{12} may occur in patients who have undergone extensive resection of the terminal ileum related to complicated meconium ileus. Some will need lifelong treatment of 100 μg of B_{12} per month, administered via the parenteral route. Vitamin C supplementation may be necessary for those at risk of deficiency due to low dietary intake of vitamin C-rich foods (especially vegetables and fruits). In these cases, dietary guidance should be given, and if deficiency persists, a vitamin C supplement is appropriate.

Guideline: Folic acid

- For women planning to become pregnant, we recommend a daily supplement of 400 mcg of folic acid in the preconceptional period and throughout the first trimester of pregnancy. (Grade of evidence: **low**)

3.7. Treatment of pancreatic insufficiency

PERT is vital to maintain adequate nutritional status; the efficacy of this treatment is well established [8,29,62,63,97,149–154]. PERT involves oral administration of pancreatic enzymes, especially protease and lipase, in order to have enzymes in the duodenal lumen for digestion of proteins and fat delivered by gastric emptying [155].

Pancreatic enzymes are usually given orally as enteric-coated tablets or microspheres, thus preventing their inactivation by gastric acid and ensuring delivery of active enzymes to the duodenum [156]. Enteric-coated microspheres may be more effective than enteric-coated tablets [8]. Addition of proton pump inhibitors may improve effectiveness of PERT. Our consensus doses are consistent with those of the North American CF Foundation guidelines for lipase intake by age of the patient, by body weight, and by grams of fat ingested per day (Table 12); for infants [62], these doses are also consistent with another recent European consensus guideline [63].

In clinical practice, administration of enzyme microspheres to infants can be difficult. If the infant refuses to take the enzyme microspheres from a spoon with a little expressed breast milk or formula, administration with an acidic puree e.g. applesauce may be successful. If the infant still refuses the microspheres the use of unprotected powder enzymes may temporarily need to be considered. Pancreatic enzymes should never be added to the infants' feed. For patients of all ages, powder enzymes can be used to help digest enteral tube feedings, e.g., when oral administration of enzymes is not possible, or when jejunostomy feeds are required. Enzymes given in this situation should not be mixed with the feed; they should be administered as bolus doses through the enteral feeding tube. When unprotected powder enzymes are used addition of a proton pump inhibitor may help to prevent destruction of lipase by gastric acid. For small children, enteric coated pancrelipase enzyme preparations have been shown to be safe, effective and preferred by parents [151,157–161].

There is no evidence on the optimum time to start treatment or on how to adjust dosages of enzymes for people with different severity of pancreatic insufficiency; well-designed trials are needed to answer these questions [8].

For those being treated with PERT, we recommend monitoring at growth and/or nutritional status at regular intervals to determine the adequacy of treatment [32] – at every clinic visit for infants, every 3 months for older children and adolescents, and every 6 months for adults.

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Guidelines: Pancreatic enzyme replacement therapy

- We recommend pancreatic enzyme replacement therapy (PERT) for all patients who have evidence of pancreatic insufficiency.
- We recommend monitoring of growth and/or nutritional status at regular intervals to determine the adequacy of PERT; monitor at every clinic visit for infants, every 3 months for older children and adolescents, and every 6 months for adults.

(Grade of evidence: **low**)

4. Feeding undernourished people with CF

Malnutrition, as defined in Table 13, remains a problem for many people with CF despite the continued improvement in respiratory and nutritional management over recent decades [29,30]. People with CF should be monitored frequently, and growth and nutritional status assessed (see *Assessment of nutritional status*) so that deficits can be identified and treated early. Impairment of growth despite adequate PERT and lung treatment can be attributed to insufficient overall energy intake but can also suggest EFA deficiency [162–164]. Nutrition support should be tailored to individual patient needs, taking into account age, nutritional and pancreatic status, home setting, religious and cultural dietary beliefs, and food preferences.

Controlled studies measuring efficacy of interventions for malnutrition in CF are limited or lacking, as highlighted in Cochrane reviews [7,165]. In absence of data, current nutrition guidelines from Europe, the UK, and the US [9–11], and this guideline provide recommendations for prevention strategies based primarily on expert consensus.

4.1. Progression and intensified feeding

Earlier nutrition guidelines used weight, stature, and weight for stature as cut off or decision points for determining when to intensify nutrition intervention [9,11,65]. More recently, Stallings et al. recommended using BMI percentiles (children) and BMI values (adults) as more accurate predictors of nutritional risk, and these guidelines adopt that approach for decision points (Table 13) [29]. Other triggers for anticipatory nutrition guidance and/or intervention are patients who are at risk of energy imbalance, experience recurrent pulmonary infections, or are entering periods of rapid growth [38].

It is important to address factors that contribute to malnutrition. These include chronic bacterial infection of the lungs, impaired glucose tolerance, and disorders likely to decrease energy intake (e.g., gastro-esophageal reflux disease/esophagitis, recurrent abdominal pain, celiac or Crohn's disease, eating pattern disorders, and depression).

A single evaluation of weight-for-length or BMI percentiles (BMIp) should be used only to screen children for nutritional risk using the cut-off proposed in Table 13. However, this approach does not provide a complete picture of the child's growth. Serial measurements over time are more informative and reflect the child's growth pattern [166]. A sharp decline or flattening of the curve could be considered a signal of failure-to-thrive, except in the first 2 years of life and in puberty, when crossing percentile curves may be normal.

Guidelines: Nutrition intervention

- We recommend nutrition intervention based on a full review of nutrition status, including a detailed review of pancreatic enzyme replacement therapy (PERT), and correction of any underlying medical conditions. (Grade of evidence: **high**)
- We recommend using age-appropriate BMI-related thresholds for deciding when to advance nutrition intervention (Table 13). (Grade of evidence: **high**)
- We recommend a progressive approach to intensification of nutrition interventions as needs increase: preventive nutritional counseling, dietary modification and/or oral nutrition supplements, and enteral tube feeding. (Grade of evidence: **low**)

4.1.1. Diet modification

4.1.1.1. Infants. Energy intake should be increased for breastfed infants who have poor weight gain despite efforts to optimize PERT, by providing more frequent feedings and fortifying expressed breast milk [25]. For formula fed infants, energy and protein intake can be increased by using high-energy/protein infant formula or considering a more concentrated feed, providing the latter is carefully supervised by a physician or CF dietitian. If linoleic acid is supplied, the general energy intake may not need to be increased [164].

4.1.1.2. Children and adults. Undernourished children and adults can increase their energy intake by eating more or more often, by fortifying food (i.e., add extra oil or fat), and by consuming more calorie-dense foods. These patients should be encouraged to eat a high fat diet with the liberal use of high fat snacks if weight gain is poor. CF dietitians can give advice on foods that can enhance weight gain, including the addition of linoleic-rich vegetable oils, butter, oil, cheese and cream to foods. Encouraging small frequent meals and snacks can also help. Linoleic acid supplementation may reduce the need for general high-energy supplements [168]. As discussed in previous sections, there are concerns that increased energy intake results in increased consumption of some dietary saturated fats and trans fatty acids, which may potentially increase risk of cardiovascular disease [17,24,84,169]. Preference should be given to fats with unsaturated fatty acids to avoid the potential risk.

Table 12
Pancreatic enzyme lipase replacement therapy: consensus guidelines [11,62,63].

Age	Suggested supplementation
Infants (up to 12 months)	2000–4000 U lipase/120 mL formula or estimated breast milk intake and approximately 2000 U lipase/gram dietary fat in food
Children 1–4 years	2000–4000 U lipase/gram dietary fat, increasing dose upward as needed (maximum dose 10,000 U lipase/kg per day)
Children >4 years and adults	Consider starting at 500 U lipase/kg/meal, titrating upward to a maximal dose of: • 1000–2500 U lipase/kg per meal, *or* • 10,000 U lipase/kg per day, *or* • 2000–4000 U lipase/gram dietary fat taken with all fat-containing meals, snacks and drinks

Abbreviation: U, units.

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Guideline: Dietary intake

- We recommend that undernourished people with CF increase their energy intake by dietary modification as a first step to achieving adequate energy intake. (Grade of evidence: **low**)

4.1.2. Behavioral intervention

Dietary counseling is essential throughout early childhood when long-term feeding habits are being established. All young children are sometimes reluctant to try new foods, and have negative interactions with their parents during mealtimes. Left uncorrected, feeding problems may develop, which can jeopardize the child's caloric intake [78–81].

Providing parents with behavioral strategies and nutrition education has been shown to be more effective in improving energy intake and growth of children than nutrition education alone [10,11,29,62,170–173]. Some of these strategies include limiting mealtimes to 15 min for toddlers, using mini-meals, and complimenting appropriate eating behaviors [62]. Coordinated advice from a behavioral counselor and a dietitian can be very helpful.

Body image issues are a problem among young people with CF—including children, adolescents, and young adults—particularly those also receiving enteral tube feeding [174]. Formal eating disorders are uncommon in patients with CF, though disturbed eating patterns are reported [175]. While enteral tube feeding may alter a young person's body image, there are also reports of improved lung function and quality of life with gastrostomy placement [43,176].

Guideline: Nutrition education and dietary counseling

- To promote weight gain and growth, we recommend nutrition education and counseling for children with CF and their parents, as well as for adults with CF. (Grade of evidence: **high**)

4.1.3. Oral nutritional supplements (ONS)

Oral nutritional supplements (ONS) may be beneficial for patients whose nutritional status remains poor despite efforts to encourage a higher dietary intake, address any related health factors or behavioral concerns that could contribute to malnutrition, and optimize PERT [29,32,65].

A recent review of three randomized clinical trials (total of 131 patients) found ONS do not promote additional weight gain in moderately malnourished children with CF compared to dietary advice and monitoring alone [7]. The use of oral nutritional supplements in adults with CF has not been adequately studied. Given the limited evidence, results of the Cochrane review should be interpreted with caution and do not mean that these supplements are not beneficial to all patients. In clinical practice, short term use of individually prescribed supplements have been shown to increase energy intake and weight in undernourished patients [163,177,178]. Furthermore, supplements may also be used to improve the status of specific nutrients e.g., EFA [163,179,180].

To ensure ONS provide additional nutrition and does not replace meals, attention to quantity and timing of supplement intake is important. The wide variety of forms and flavors now available improves the likelihood of finding a product that appeals to personal preferences, and minimizes taste fatigue often reported with long term supplement use.

Guideline: Oral nutrition supplements

- We recommend clinicians consider the use of oral nutritional supplements for treating children and adults who fail to achieve optimal growth rates and nutritional status with oral dietary intake and pancreatic enzyme replacement therapy (PERT) alone. (Grade of evidence: **low**)
- We recommend clinicians regularly review and re-evaluate patients who are taking oral nutritional supplements to determine whether the patient should continue taking them. (Grade of evidence: **high**)

4.1.4. Tube-feeding (enteral nutrition)

When an oral diet and supplements fail to achieve adequate nutritional status, many CF centers use enteral tube feeding. Use of tube feeding reportedly improves weight gain, nutritional status [165,181–186], and respiratory status [165,181,183,184,187]. Despite the widespread use of tube feeding for people with CF, the efficacy of this feeding method on clinical outcomes has not been assessed by randomized control trials [165].

The route, formula, and timing for enteral feeding are determined by the patient's preference and clinical status. Gastrostomy feeding is usually preferred to nasogastric tubes for long-term nutritional support. It is helpful to thoroughly explain feeding needs and choices to the patient in order to increase the likelihood of success. Feeds are usually introduced gradually as tolerated and administered as continuous infusions overnight, bolus feeds (gravity or pump assisted) during the day, or a combination of both. With nocturnal feeds, it is possible to encourage patients to eat a high-energy diet during the day. Most patients tolerate a high-energy polymeric feed (1.5–2 kcal/mL). If this is not well tolerated, an elemental or semi-elemental feed may be beneficial. Polymeric feeds necessitates PERT, as do semi-elemental feeds given to severely PI patients [97], with dosing and time individually

Table 13
Feeding undernourished people with CF: consensus guidelines [11,29,167].

Nutritional status and intervention	Decision point for intensified nutritional support		
	Infants ≤ 2 years	Children 2–18 years	Adults > 18 years
Normal nutritional status: ***Preventive nutritional counseling***	Weight and length ≥ 50th percentile	BMIp ≥ 50th percentile	• BMI: 18.5 to 22 (for females) 18.5 to 23 (for males), or • No weight loss
Special nutritional support for impaired nutritional status: ***Diet modification and/or oral nutrition supplements***	Failure to thrive: weight and length 10th to 50th percentile	• BMIp 10th to 50th, or • Weight loss in previous 2–4 months, or • No weight gain in previous 2 months	• BMI < 18.5, or • Weight loss of 5% in previous 2 months
Persistent undernutrition: ***Enteral tube feeding***	Persistent failure to thrive weight and length < 10th percentile	• Persistently low BMIp (BMIp < 10th), or • Weight loss of 2 percentile points since last visit and stunting of growth	• Persistently low BMI (BMI < 18.5), or • Continuing weight loss (>5%) and stunting of growth

Abbreviations: BMI, Body Mass Index in kg/m^2; BMIp: Body Mass Index percentile.

calibrated. PERT is usually given at the beginning and end of the feed but new devices for the administration of PERT are being developed; bolus feeds may need a higher dose due to the increased rate of fat infusion. Patients should be monitored for glucose intolerance; a small dose of insulin may be required to manage the feed [10].

Guidelines: Enteral nutrition

- We recommend that clinicians consider the use of polymeric enteral tube feeding when oral interventions have failed to achieve acceptable rates of growth and nutritional status. (Grade of evidence: **high**)
- We recommend basing route, formula, and timing for enteral feeding selection on individual needs and preferences. (Grade of evidence: **low**)

4.1.5. Parenteral nutrition

Parenteral nutrition is not routinely recommended as a method of nutritional support for patients with CF due to the risk of complications, difficulty of administration and high cost [10]. Parenteral feeding may be essential as short-term nutritional support following intestinal resection in infants presenting with meconium ileus [10,25] and children and adults following major GI surgery where enteral feeding is not possible. It may also be beneficial for severely compromised patients awaiting transplantation [11]. Early enteral feeding should always be encouraged to reduce the risk of cholestasis.

Guideline: Parenteral nutrition

We recommend the use of parenteral nutrition be reserved for exceptional cases when enteral feeding is not possible. (Grade of evidence: **low**)

4.2. CF-related disease with nutritional consequences

4.2.1. GI complications

Some gastrointestinal complications of CF require special consideration and nutritional treatments. These include meconium ileus, distal intestinal obstruction syndrome, constipation, cirrhosis and portal hypertension, recurrent pancreatitis, gastro-esophageal reflux disease and combined occurrence of conditions such as celiac disease, cows' milk protein intolerance, lactose intolerance, and inflammatory bowel disease [11,188,189]. In these cases, additional diagnostic gastrointestinal work-up is warranted, and individualized nutritional treatment is appropriate.

4.2.2. Bone disease

Osteopenia and osteoporosis are common among adolescents and adults with CF [56]. Reduced bone mineral density (BMD) with increased fracture risk is of concern in this population [56,58,190,191]. Low BMD can also occur in children [192]. Low BMD has been associated with reduced working capacity [193], low fat mass but normal lean body mass [194], severe lung disease [56], and a fatty acid pattern that reflects EFA insufficiency [194,195]. Glucocorticoid treatment is a strong risk factor for decreased bone mass [196,197].

The main indicators of nutritional risk are poor nutritional status; delayed puberty; and deficiencies of vitamin D, calcium and vitamin K [57,70,71,198].

As discussed in section 1, we emphasize routine monitoring of bone health using DXA for all CF patients from 8 to 10 years of age. For patients younger than 20 years of age whose height is more than one standard deviation below age- and sex-matched healthy controls, BMD Z score should be adjusted for height or statural age to avoid over estimating deficits in BMD in people with short stature [71].

We recommend treatment by provision of adequate calcium, vitamin D, and vitamin K [71,90]. Supplemental treatments for calcium and vitamins D and K have been discussed previously in section 2. In section 4, we discuss bisphosphonates as part of treatment for osteoporosis.

We suggest people with CF routinely engage in weight-bearing exercise, as physical activity is strongly correlated with increased bone mineral density [90,197]. Children and adolescents should be encouraged to exercise (high impact weight bearing physical activities) for 20–30 min three times a week in addition to their usual activities [71]. Adults should be encouraged to perform regular weight bearing and resistance activities [71].

Guideline: Bone disease

- For CF patients with osteopenia or osteoporosis, we recommend nutritional intervention to achieve normal weight gain and growth in children and an optimal body weight in adults, including intake of calcium-rich foods and a balanced fatty acid diet. Provision of supplemental calcium, vitamin D, and vitamin K may be necessary. (Grade of evidence: **moderate**)
- We recommend that people with CF routinely engage in weight-bearing exercise. (Grade of evidence: **low**)
- We recommend assessment of bone health (DXA), including, for all patients $\geq$ 8 years old, every 1–5 years, depending on the age of the patient, value of the previous scan, and presence of risk factors. (Grade of evidence: **low**)

4.2.3. CF-related diabetes

In CF, the endocrine pancreas is also affected over time, particularly the β-cells that produce insulin; many people with CF eventually develop CF-related diabetes (CFRD) due to insulin deficiency [53]. The prevalence of CFRD increases with age, so more than half of all patients over 40 years are affected [199]. Higher blood glucose levels promote bacterial colonization in the lungs [53]. As a result, CFRD adversely affects pulmonary function and increases risk for mortality. For these reasons, we recommend annual screening of CF patients $\geq$10 years for glucose tolerance. In a 2-h oral glucose tolerance test, a final plasma glucose level $\geq$200 mg/dL (>11.1 mmol/L) determines the diagnosis of diabetes. Plasma glucose elevation $\geq$200 mg/dL at 1 h but normalization at 2 h is recognized as indeterminate glycemia, an indicator of high risk for eventual diabetes [200].

For people with CF and diabetes, we suggest care managers pay attention to the multiple nutrition concerns of energy adequacy, glycemic control, and attention to risk of cardiovascular disease. As such, the American Diabetes Association, the Cystic Fibrosis Foundation, and the Pediatric Endocrine Society advise: higher than standard intake of calories (1.2–1.5 times dietary reference values for age with individualization for weight gain and BMI); carbohydrate intake individualized and monitored for glycemic control, limited use of artificial sweeteners due to need for adequate calories; higher than standard protein intake; and high fat diet as needed for EFA compensation and weight maintenance [201].

Treatment for CFRD also includes education on diabetes self-management, insulin therapy, and aerobic exercise [201]. There is only limited evidence for use of oral hypoglycemic agents in CFRD [201], so we suggest insulin therapy as the treatment of choice [32]. In the management of CFRD the use of a bolus insulin regimen is

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suggested. Patients need to learn to adjust their insulin dose to the carbohydrate content of the meal.

Incretins or incretin-mimetic agents may have a role in the future, but more studies are needed for evidence-based recommendations [36]. There is now evidence that CF patients with pancreatic insufficiency are at risk for developing dyslipidemia [142]; this evidence suggests that the traditional focus on high-carbohydrate, high-fat diet for CF may need to be adjusted as people with CF are living longer, and focus on quality of fat more than quantity.

CFRD patients can benefit from being seen periodically by a specialized team with expertise in diabetes and CF [32].

Guideline: CF-related diabetes

- We recommend annual screening of all CF patients ≥ 10 years for glucose tolerance.
- For all patients diagnosed with cystic fibrosis-related diabetes or impaired glucose tolerance, we recommend education on self-management of the conditions, moderate aerobic exercise, and prescription of insulin as needed.
- Based on published guidelines for cystic fibrosis-related diabetes nutrition care, we recommend care managers pay attention to the multiple nutrition concerns of energy adequacy, glycemic control, and possible cardiovascular risk.
- We recommend that cystic fibrosis-related diabetes patients be seen regularly by a specialized team with expertise in diabetes and CF.

(Grade of evidence: **low**)

4.2.4. Liver disease

Approximately 5–10% of CF patients develop multi-lobular cirrhosis during the first decade of life [202]. Many CF patients later develop signs of portal hypertension with complications such as variceal bleeding. We suggest considering supplementation of EFAs and fat-soluble vitamins because there is commonly an association between liver disease and hepatic steatosis [54,203].

Older children and adults with CF may experience liver failure. Impaired liver function is associated with worsening pulmonary function. Liver transplantation is a treatment option that may promote improvement of nutritional status [37,204].

Guideline: Liver disease

We suggest considering supplementation of essential fatty acids and fat-soluble vitamins in CF patients with liver disease and hepatic steatosis. (Grade of evidence: **moderate**)

5. Specialized nutrition-related treatments

In the following section, we review what is currently known about other treatments for nutritional issues in CF, i.e., studies on dietary supplementation of certain fatty acids and on treatments with anti-osteoporotic and anabolic agents or on use of probiotics. We call on researchers to design and conduct studies on these and other new treatments for nutritional complications of CF.

We do not make CF-specific recommendations on dietary supplementation of certain fatty acids, or on treatments with anti-osteoporotic agents, anti-inflammatory agents, anabolic therapies, or probiotics, as evidence is not sufficient to do so and the risk-to-benefit ration may be too high.

5.1. Essential fatty acids

Two fatty acids are known to be essential for humans: alpha linolenic acid (ALA, an omega-3 fatty acid) and linoleic acid (LA, an omega-6 fatty acid). Some other fatty acids are classified as conditionally essential, meaning that they become essential under some developmental or disease conditions, i.e. DHA (an omega-3 fatty acid) and arachidonic acid (AA, an omega-6 fatty acid).

For more than five decades, altered fatty acid profiles have been reported in infants and children with CF [162,205–210]. The mechanisms underlying these abnormal fatty acid profiles remain incompletely understood [55,162,208,211–213]. A connecting link between abnormal fatty acid levels and CFTR membrane protein deficiency is not known [26,206,211].

In infants and children with CF, low EFA levels are not necessarily accompanied by usual clinical signs, e.g., dermatitis and learning disabilities. However, low LA was reported to correlate with poor pulmonary status and impaired growth in infants and children [162,164,214,215], while low DHA with high AA (i.e., high AA to DHA ratio) was associated with impaired bone mineral density in both children and young adults with CF [194,195]. Altered levels of EFA were likewise correlated with impaired renal, hepatic, and immune function [162,211,212,216,217]. Based on current evidence, EFA deficiency can be determined by measuring the level of linoleic acid level or triene:tetraene (T3:T4) [162,210].

Results of a small number of studies suggest that dietary repletion of EFA may improve lung function [55,180,210,214,218,219]. In addition, regular omega-3 supplements may provide some anti-inflammatory benefits with relatively few adverse effects for people with CF [180,216,219,220].

However, because evidence is still not sufficient [221], we are not able to make specific practice recommendations regarding dietary supplementation of fatty acids for improved lung function or anti-inflammatory effects in children or adults with CF. Well-designed prospective studies are necessary to confirm and extend these preliminary findings.

5.2. Anti-osteoporotic agents

Treatment with bisphosphonate agents increases bone mineral density and decreases the risk of new fractures in post-menopausal women and in people receiving long-term oral corticosteroids. Since bone weakening is common among older children and adults with CF, it is therefore important to determine whether bisphosphonate therapy likewise yields benefits for CF patients.

Clinical trials have investigated bisphosphonate treatment for adults and children with CF. A meta-analysis of 6 trials of bisphosphonate therapy for adults with CF showed significant increases in bone mineral density of the lumbar spine and hip regions after 6, 12, or 24 months of treatment (compared to untreated control patients) [4]. However, the analysis found no differences for fracture rates or deaths, likely because the study populations were too small [4]. Results of a recent prospective, randomized controlled trial showed that the bisphosphonate alendronate was safe and effective for increasing bone density in children, adolescents, and young adults with CF; such results suggest the possibility of using bisphosphonate therapy to prevent bone loss in young CF patients [222].

Bone weakening leading to brittle bones has a marked negative impact on quality of life; low bone mineral density can be readily diagnosed with DXA [223]. For these reasons, bisphosphonate treatment is a practical and potentially valuable treatment for CF patients with low bone density. However, individuals who take bisphosphonate medications sometimes experience bone pain and flu-like symptoms [4]. The European Cystic Fibrosis guidelines

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recommend bisphosphonate treatment for children and adults who have bone mineral density Z-score lower than −2; bisphosphonate treatment is also recommended for adults with >4% bone loss per year on serial DXA and for those with a history of low-trauma spinal or extremity fractures [71]. Because of long term safety concerns, use of bisphosphonate treatment in children remains controversial [224].

While we do not make absolute recommendations of bisphosphonate treatment for CF patients with or at risk of low bone mineral density, we recognize that some patients will benefit.

Guideline: Anti-osteoporotic agents

We suggest that clinicians consider benefits versus risks when making decisions about use of bisphosphonates by CF patients for prevention or treatment of low bone mineral density. (Grade of evidence: **moderate**)

5.3. Growth hormone

Many individuals with CF do not achieve normal linear growth or predicted adult height [225] and experience poor weight gain and reduced lean body mass [226]. As a result, anabolic agents such as growth hormone (GH) may eventually play roles in CF treatment [2,227,228].

Pulmonary function and growth parameters were improved in patients treated with growth hormone, as reported in a systematic review that included 10 controlled trials and 8 observational studies [227]. Results showed that recombinant human GH improved almost all intermediate measures of pulmonary function, height, and weight in children and adolescents with CF; GH also appeared to have positive effects on bone mineral content [227]. Further, a recent trial evaluated 12-month treatment with growth hormone in patients with reduced growth and bone age (multicenter, randomized, controlled); results showed significant effects of growth hormone on improving both growth and lung volumes [228]. Positive effects of growth hormone on long-term health outcomes such as quality of life or mortality have not yet been demonstrated [229].

5.4. Appetite stimulants

Because patients with CF and their families are concerned about poor appetite, appetite stimulants have been used to help CF patients increase the amounts they eat so they gain weight and improve overall health. While appetite stimulants offer potential benefits, there are concerns that they may have side effects. A recent meta-analysis of 3 studies examined efficacy and safety of specific appetite stimulants [2]; this analysis included 2 studies of megestrol acetate [230,231] and a study of cyproheptadine hydrochloride [232]. In the short term (six months) in adults and children, appetite stimulants improved weight (or weight z score) and appetite, with no difference between megestrol acetate and cyproheptadine; side effects were insufficiently reported to determine the full extent of their impact. A newer study on cyproheptadine has since been published, and results of this study showed a clinically relevant effect size for weight/age (z score) and body mass index for age (z score) [233]. Taken together, all studies were small in size and had moderate-grade evidence. As a result, we are not able to offer an evidence-based guideline on use of appetite stimulants for CF patients [11].

5.5. Probiotics

CF is characterized by recurrent pulmonary inflammation and infections, which begin early in childhood and eventually lead to morbidity and mortality due to respiratory failure. Probiotics are orally-administered live bacteria, which have been used to decrease severity of acute gastroenteritis in children [234,235]. Evidence continues to build for probiotic use by CF patients. In pilot studies, *Lactobacillus* GG treatments for 1–6 months lowered markers of inflammation [236], decreased pulmonary exacerbation rates, and lowered the frequency of hospital admissions [237,238]. These 3 pilot studies were small in size, so we are not yet able to provide an evidence-based guideline. However, use of probiotics for prevention and treatment of pulmonary inflammation in CF patients is a promising area for further investigation.

6. Conclusions

The discovery and cloning of the CFTR gene 25 years ago led to the identification of the structure and function of the CFTR chloride channel [239,240]. In turn, new targeted therapies were developed as a result of better understanding of CF molecular mechanisms and usual disease progression. Current CF treatments variously target respiratory infections, inflammation, and mucus clearance. With these *ESPEN-ESPGHAN-ECFS Guidelines on Nutrition Care*, we underscore the importance of nutrition along with these other treatments to extend survival and to improve quality of life for children and adults with CF.

Conflict of interest

No conflict of interest.

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References

[1] Bonifant CM, Shevill E, Chang AB. Vitamin A supplementation for cystic fibrosis. Cochrane Database Syst Rev 2014;5:CD006751.
[2] Chinuck R, Dewar J, Baldwin DR, Hendron E. Appetite stimulants for people with cystic fibrosis. Cochrane Database Syst Rev 2014;7:CD008190.
[3] Ciofu O, Lykkesfeldt J. Antioxidant supplementation for lung disease in cystic fibrosis. Cochrane Database Syst Rev 2014;8:CD007020.
[4] Conwell LS, Chang AB. Bisphosphonates for osteoporosis in people with cystic fibrosis. Cochrane Database Syst Rev 2014;3:CD002010.
[5] Ferguson JH, Chang AB. Vitamin D supplementation for cystic fibrosis. Cochrane Database Syst Rev 2014;5:CD007298.
[6] Okebukola PO, Kansra S, Barrett J. Vitamin E supplementation in people with cystic fibrosis. Cochrane Database Syst Rev 2014;12:CD009422.
[7] Smyth RL, Rayner O. Oral calorie supplements for cystic fibrosis. Cochrane Database Syst Rev 2014;11:CD000406.
[8] Somaraju UR, Solis-Moya A. Pancreatic enzyme replacement therapy for people with cystic fibrosis. Cochrane Database Syst Rev 2014;10:CD008227.
[9] Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2002;35:246–59.
[10] Cystic Fibrosis Trust. Nutritional management of cystic fibrosis. Bromley, UK: Cystic Fibrosis Trust; 2002.
[11] Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman HG, et al. Nutrition in patients with cystic fibrosis: a European Consensus. J Cyst Fibros 2002;1:51–75.
[12] Preiser JC, Schneider SM. ESPEN disease-specific guideline framework. Clin Nutr 2011;30:549–52.
[13] Petrie G, Barnwell E, Grimshaw J, on behalf of the Scottish Intercollegiate Guidelines Network. Clinical guidelines: criteria for appraisal for national use. Edinburgh: Royal College of Physicians; 1995.

[14] Agency for Health Care Policy and Research. Acute pain management, operative or medical procedures and trauma Rockville, MD, USA. 1992. p. 92–0032.
[15] Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
[16] Edenborough FP, Borgo G, Knoop C, Lannefors L, Mackenzie WE, Madge S, et al. Guidelines for the management of pregnancy in women with cystic fibrosis. J Cyst Fibros 2008;7(Suppl. 1):S2–32.
[17] Smith C, Winn A, Seddon P, Ranganathan S. A fat lot of good: balance and trends in fat intake in children with cystic fibrosis. J Cyst Fibros 2012;11:154–7.
[18] Culhane S, George C, Pearo B, Spoede E. Malnutrition in cystic fibrosis: a review. Nutr Clin Pract 2013;28:676–83.
[19] FitzSimmons SC. The changing epidemiology of cystic fibrosis. J Pediatr 1993;122:1–9.
[20] Southern KW, Munck A, Pollitt R, Travert G, Zanolla L, Dankert-Roelse J, et al. A survey of newborn screening for cystic fibrosis in Europe. J Cyst Fibros 2007;6:57–65.
[21] Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cyst Fibros 2008;7:450–3.
[22] Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. Am J Respir Crit Care Med 2011;183:1463–71.
[23] Li L, Somerset S. Digestive system dysfunction in cystic fibrosis: challenges for nutrition therapy. Dig Liver Dis 2014;46:865–74.
[24] Engelen MP, Com G, Deutz NEP. Protein is an important but undervalued macronutrient in the nutritional care of patients with cystic fibrosis. Curr Opin Clin Nutr Metab Care 2014;17:515–20.
[25] Kalnins D, Wilschanski M. Maintenance of nutritional status in patients with cystic fibrosis: new and emerging therapies. Drug Des Devel Ther 2012;6:151–61.
[26] Strandvik B. Fatty acid metabolism in cystic fibrosis. Prostagl Leukot Essent Fat Acids 2010;83:121–9.
[27] Gaskin KJ. Nutritional care in children with cystic fibrosis: are our patients becoming better? Eur J Clin Nutr 2013;67:558–64.
[28] Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. J Clin Epidemiol 1988;41:583–91.
[29] Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc 2008;108:832–9.
[30] McCormick J, Mehta G, Olesen HV, Viviani L, Macek Jr M, Mehta A, et al. Comparative demographics of the European cystic fibrosis population: a cross-sectional database analysis. Lancet 2010;375:1007–13.
[31] Maqbool A, Schall JI, Gallagher PR, Zemel BS, Strandvik B, Stallings VA. Relation between dietary fat intake type and serum fatty acid status in children with cystic fibrosis. J Pediatr Gastroenterol Nutr 2012;55:605–11.
[32] Smyth AR, Bell SC, Bojcin S, Bryon M, Duff A, Flume P, et al. European cystic fibrosis Society standards of care: best practice guidelines. J Cyst Fibros 2014;13(Suppl. 1):S23–42.
[33] Stephenson AL, Mannik LA, Walsh S, Brotherwood M, Robert R, Darling PB, et al. Longitudinal trends in nutritional status and the relation between lung function and BMI in cystic fibrosis: a population-based cohort study. Am J Clin Nutr 2013;97:872–7.
[34] Zolin A, McKone E, van Rens J, Fox A, Iansa P, Preftitsi A, et al. ECFSPR annual report 2010. Karup, Denmark: European Cystic Fibrosis Society; 2014.
[35] Cystic Fibrosis Foundation Patient Registry. 2011 annual data report. Bethesda, Maryland: Cystic Fibrosis Foundation; 2011.
[36] Perano S, Rayner CK, Couper J, Martin J, Horowitz M. Cystic fibrosis related diabetes-a new perspective on the optimal management of postprandial glycemia. J Diabetes Complicat 2014;28:904–11.
[37] Debray D, Kelly D, Houwen R, Strandvik B, Colombo C. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. J Cyst Fibros 2011;10(Suppl. 2):S29–36.
[38] Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol 2006;20:531–46.
[39] Vaisman N, Pencharz PB, Corey M, Canny GJ, Hahn E. Energy expenditure of patients with cystic fibrosis. J Pediatr 1987;111:496–500.
[40] Castro M, Diamanti A, Gambarara M, Bella S, Lucidi V, Papadatou B, et al. Resting energy expenditure in young patients with cystic fibrosis receiving antibiotic therapy for acute respiratory exacerbations. Clin Nutr 2002;21:141–4.
[41] Mc Closkey M, Redmond AO, Mc Cabe C, Pyper S, Westerterp KR, Elborn SJ. Energy balance in cystic fibrosis when stable and during a respiratory exacerbation. Clin Nutr 2004;23:1405–12.
[42] Elborn JS. How can we prevent multisystem complications of cystic fibrosis? Semin Respir Crit Care Med 2007;28:303–11.
[43] Morton AM. Symposium 6: young people, artificial nutrition and transitional care. The nutritional challenges of the young adult with cystic fibrosis: transition. Proc Nutr Soc 2009;68:430–40.
[44] Doring G, Flume P, Heijerman H, Elborn JS, G.. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. J Cyst Fibros 2012;11:461–79.
[45] Greer R, Shepherd R, Cleghorn G, Bowling FG, Holt T. Evaluation of growth and changes in body composition following neonatal diagnosis of cystic fibrosis. J Pediatr Gastroenterol Nutr 1991;13:52–8.
[46] Konstan MW, Butler SM, Wohl ME, Stoddard M, Matousek R, Wagener JS, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. J Pediatr 2003;142:624–30.
[47] Koscik RL, Farrell PM, Kosorok MR, Zaremba KM, Laxova A, Lai HC, et al. Cognitive function of children with cystic fibrosis: deleterious effect of early malnutrition. Pediatrics 2004;113:1549–58.
[48] Vieni G, Faraci S, Collura M, Lombardo M, Traverso G, Cristadoro S, et al. Stunting is an independent predictor of mortality in patients with cystic fibrosis. Clin Nutr 2013;32:382–5.
[49] Shoff SM, Tluczek A, Laxova A, Farrell PM, Lai HJ. Nutritional status is associated with health-related quality of life in children with cystic fibrosis aged 9–19 years. J Cyst Fibros 2013;12:746–53.
[50] Alicandro G, Frova L, Di Fraia G, Colombo C. Cystic fibrosis mortality trend in Italy from 1970 to 2011. J Cyst Fibros 2015;14:267–74.
[51] Alicandro G, Battezzati PM, Battezzati A, Speziali C, Claut L, Motta V, et al. Insulin secretion, nutritional status and respiratory function in cystic fibrosis patients with normal glucose tolerance. Clin Nutr 2012;31:118–23.
[52] Lanng S, Thorsteinsson B, Nerup J, Koch C. Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. Eur J Pediatr 1992;151:684–7.
[53] Waugh N, Royle P, Craigie I, Ho V, Pandit L, Ewings P, et al. Screening for cystic fibrosis-related diabetes: a systematic review. Health Technol Assess 2012;16. iii–iv, 1–179.
[54] Lindblad A, Glaumann H, Strandvik B. Natural history of liver disease in cystic fibrosis. Hepatology 1999;30:1151–8.
[55] Peretti N, Marcil V, Drouin E, Levy E. Mechanisms of lipid malabsorption in Cystic Fibrosis: the impact of essential fatty acids deficiency. Nutr Metab (Lond) 2005;2:11.
[56] Conway SP, Morton AM, Oldroyd B, Truscott JG, White H, Smith AH, et al. Osteoporosis and osteopenia in adults and adolescents with cystic fibrosis: prevalence and associated factors. Thorax 2000;55:798–804.
[57] Legroux-Gerot I, Leroy S, Prudhomme C, Perez T, Flipo RM, Wallaert B, et al. Bone loss in adults with cystic fibrosis: prevalence, associated factors, and usefulness of biological markers. Jt Bone Spine 2012;79:73–7.
[58] Javier RM, Jacquot J. Bone disease in cystic fibrosis: what's new? Jt Bone Spine 2011;78:445–50.
[59] Lai HC, Kosorok MR, Laxova A, Davis LA, FitzSimmon SC, Farrell PM. Nutritional status of patients with cystic fibrosis with meconium ileus: a comparison with patients without meconium ileus and diagnosed early through neonatal screening. Pediatrics 2000;105:53–61.
[60] Yen EH, Quinton H, Borowitz D. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. J Pediatr 2013;162. 530–535 e531.
[61] Giglio L, Candusso M, D'Orazio C, Mastella G, Faraguna D. Failure to thrive: the earliest feature of cystic fibrosis in infants diagnosed by neonatal screening. Acta Paediatr 1997;86:1162–5.
[62] Cystic Fibrosis Foundation, Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr 2009;155:S73–93.
[63] Sermet-Gaudelus I, Mayell SJ, Southern KW, European Cystic Fibrosis Society NSWG. Guidelines on the early management of infants diagnosed with cystic fibrosis following newborn screening. J Cyst Fibros 2010;9:323–9.
[64] WHO Multicentre Growth Reference Study Group. The WHO child growth standards. 2006. http://www.who.int/childgrowth/en/.
[65] Cystic Fibrosis Trust. Standards for the clinical care of children and adults with cystic fibrosis in the UK. Bromley, UK: Cystic Fibrosis Trust; December 2011.
[66] Sathe MN, Patel AS. Update in pediatrics: focus on fat-soluble vitamins. Nutr Clin Pract 2010;25:340–6.
[67] Wood LG, Gibson PG, Garg ML. Circulating markers to assess nutritional therapy in cystic fibrosis. Clin Chim Acta 2005;353:13–29.
[68] Alicandro G, Bisogno A, Battezzati A, Bianchi ML, Corti F, Colombo C. Recurrent pulmonary exacerbations are associated with low fat free mass and low bone mineral density in young adults with cystic fibrosis. J Cyst Fibros 2014;13:328–34.
[69] Ionescu AA, Nixon LS, Luzio S, Lewis-Jenkins V, Evans WD, Stone MD, et al. Pulmonary function, body composition, and protein catabolism in adults with cystic fibrosis. Am J Respir Crit Care Med 2002;165:495–500.
[70] Aris RM, Merkel PA, Bachrach LK, Borowitz DS, Boyle MP, Elkin SL, et al. Guide to bone health and disease in cystic fibrosis. J Clin Endocrinol Metab 2005;90:1888–96.
[71] Sermet-Gaudelus I, Bianchi ML, Garabedian M, Aris RM, Morton A, Hardin DS, et al. European cystic fibrosis bone mineralisation guidelines. J Cyst Fibros 2011;10(Suppl. 2):S16–23.
[72] DiMagno EP, Go VL, Summerskill WH. Relations between pancreatic enzyme ouputs and malabsorption in severe pancreatic insufficiency. N Engl J Med 1973;288:813–5.
[73] Ledder O, Haller W, Couper RT, Lewindon P, Oliver M. Cystic fibrosis: an update for clinicians. Part 2: Hepatobiliary and pancreatic manifestations. J Gastroenterol Hepatol 2014;29:1954–62.
[74] McArdle JR. Pregnancy in cystic fibrosis. Clin Chest Med 2011;32. 111–120, ix.

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[75] Robinson KA, Saldanha IJ, McKoy NA. Management of infants with cystic fibrosis: a summary of the evidence for the cystic fibrosis foundation working group on care of infants with cystic fibrosis. J Pediatr 2009;155:S94–105.
[76] Colombo C, Costantini D, Zazzeron L, Faelli N, Russo MC, Ghisleni D, et al. Benefits of breastfeeding in cystic fibrosis: a single-centre follow-up survey. Acta Paediatr 2007;96:1228–32.
[77] Kerem E, Conway S, Elborn S, Heijerman H, Consensus C. Standards of care for patients with cystic fibrosis: a European consensus. J Cyst Fibros 2005;4:7–26.
[78] Hammons AJ, Fiese B. Mealtime interactions in families of a child with cystic fibrosis: a meta-analysis. J Cyst Fibros 2010;9:377–84.
[79] Crist W, McDonnell P, Beck M, Gillespie CT, Barrett P, Mathews J. Behavior at mealtimes and the young child with cystic fibrosis. J Dev Behav Pediatr 1994;15:157–61.
[80] Duff AJ, Wolfe SP, Dickson C, Conway SP, Brownlee KG. Feeding behavior problems in children with cystic fibrosis in the UK: prevalence and comparison with healthy controls. J Pediatr Gastroenterol Nutr 2003;36:443–7.
[81] Stark LJ, Jelalian E, Powers SW, Mulvihill MM, Opipari LC, Bowen A, et al. Parent and child mealtime behavior in families of children with cystic fibrosis. J Pediatr 2000;136:195–200.
[82] EFSA Panel on Dietetic Products Nutrition and Allergies. Scientific opinion on dietary reference values for energy. EFSA J 2013;11. 3005, 112pp.
[83] Matel JL. Nutritional management of cystic fibrosis. JPEN J Parenter Enteral Nutr 2012;36:60S–7S.
[84] Woestenenk JW, Castelijns SJ, van der Ent CK, Houwen RH. Dietary intake in children and adolescents with cystic fibrosis. Clin Nutr 2014;33:528–32.
[85] Arvanitakis SN, Lobeck CC. Metabolic alkalosis and salt depletion in cystic fibrosis. J Pediatr 1973;82:535–6.
[86] Coates AJ, Crofton PM, Marshall T. Evaluation of salt supplementation in CF infants. J Cyst Fibros 2009;8:382–5.
[87] Ozcelik U, Gocmen A, Kiper N, Coskun T, Yilmaz E, Ozguc M. Sodium chloride deficiency in cystic fibrosis patients. Eur J Pediatr 1994;153:829–31.
[88] Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC Text with EEA relevance. Off J Eur Union 2006. L 401/1.
[89] Meuller D. Medical nutrition therapy for pulmonoary disease. In: Mahan L, Escott-Stump S, Raymond J, editors. Krause's food and the nutrition care process. St Louis, MO: Elsevier Saunders; 2012. p. 782–98.
[90] Cystic Fibrosis Trust. Bone Mineralisation Working Group, Bone mineralisation in cystic fibrosis. Bromley, UK: Cystic Fibrosis Trust; 2007.
[91] Schulze KJ, O'Brien K O, Germain-Lee EL, Baer DJ, Leonard AL, Rosenstein BJ. Endogenous fecal losses of calcium compromise calcium balance in pancreatic-insufficient girls with cystic fibrosis. J Pediatr 2003;143:765–71.
[92] EFSA NDA Panel (EFSA Panel on Dietetic Products Nutrition and Allergies). Scientific opinion on dietary reference values for calcium. EFSA J 2015;13(5):4101–83. doi:10.2903/j.efsa.2015.4101.
[93] Cheng S, Lyytikainen A, Kroger H, Lamberg-Allardt C, Alen M, Koistinen A, et al. Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10-12-y-old girls: a 2-y randomized trial. Am J Clin Nutr 2005;82:1115–26. quiz 1147–1118.
[94] Uijterschout L, Nuijsink M, Hendriks D, Vos R, Brus F. Iron deficiency occurs frequently in children with cystic fibrosis. Pediatr Pulmonol 2014;49:458–62.
[95] Gifford AH, Miller SD, Jackson BP, Hampton TH, O'Toole GA, Stanton BA, et al. Iron and CF-related anemia: expanding clinical and biochemical relationships. Pediatr Pulmonol 2011;46:160–5.
[96] von Drygalski A, Biller J. Anemia in cystic fibrosis: incidence, mechanisms, and association with pulmonary function and vitamin deficiency. Nutr Clin Pract 2008;23:557–63.
[97] Berry AJ. Pancreatic enzyme replacement therapy during pancreatic insufficiency. Nutr Clin Pract 2014;29:312–21.
[98] Uijterschout L, Swinkels DW, Akkermans MD, Zandstra T, Nuijsink M, Hendriks D, et al. The value of soluble transferrin receptor and hepcidin in the assessment of iron status in children with cystic fibrosis. J Cyst Fibros 2014;13:639–44.
[99] Fischer R, Simmerlein R, Huber RM, Schiffl H, Lang SM. Lung disease severity, chronic inflammation, iron deficiency, and erythropoietin response in adults with cystic fibrosis. Pediatr Pulmonol 2007;42:1193–7.
[100] Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352:1011–23.
[101] Akanli L, Lowenthal DB, Gjonaj S, Dozor AJ. Plasma and red blood cell zinc in cystic fibrosis. Pediatr Pulmonol 2003;35:2–7.
[102] Maqbool A, Schall JI, Zemel BS, Garcia-Espana JF, Stallings VA. Plasma zinc and growth status in preadolescent children with cystic fibrosis. J Pediatr Gastroenterol Nutr 2006;43:95–101.
[103] Neve J, Van Geffel R, Hanocq M, Molle L. Plasma and erythrocyte zinc, copper and selenium in cystic fibrosis. Acta Paediatr Scand 1983;72:437–40.
[104] Van Biervliet S, Van Biervliet J-P, Robberecht E, Taylor C. Importance of zinc in cystic fibrosis patients. Curr Pediatr Rev 2009;5:184–8.
[105] Griese M, Kappler M, Eismann C, Ballmann M, Junge S, Rietschel E, et al. Inhalation treatment with glutathione in patients with cystic fibrosis. A randomized clinical trial. Am J Respir Crit Care Med 2013;188:83–9.
[106] Shamseer L, Adams D, Brown N, Johnson JA, Vohra S. Antioxidant micronutrients for lung disease in cystic fibrosis. Cochrane Database Syst Rev 2010:CD007020.
[107] Winklhofer-Roob BM, Tiran B, Tuchschmid PE, van't Hof MA, Shmerling DH. Effects of pancreatic enzyme preparations on erythrocyte glutathione peroxidase activities and plasma selenium concentrations in cystic fibrosis. Free Radic Biol Med 1998;25:242–9.
[108] Gallagher M. Intake: the nutrients and their metabolism. In: Mahan L, Escott-Stump S, Raymond J, editors. Krause's food and the nutrition care process. St Louis, MO: Elsevier Saunders; 2012. p. 32–128.
[109] Dorlochter L, Aksnes L, Fluge G. Faecal elastase-1 and fat-soluble vitamin profiles in patients with cystic fibrosis in Western Norway. Eur J Nutr 2002;41:148–52.
[110] Rana M, Wong-See D, Katz T, Gaskin K, Whitehead B, Jaffe A, et al. Fat-soluble vitamin deficiency in children and adolescents with cystic fibrosis. J Clin Pathol 2014;67:605–8.
[111] Maqbool A, Stallings VA. Update on fat-soluble vitamins in cystic fibrosis. Curr Opin Pulm Med 2008;14:574–81.
[112] Carr SB, Dinwiddie R. Annual review or continuous assessment? J R Soc Med 1996;89(Suppl. 27):3–7.
[113] Feranchak AP, Sontag MK, Wagener JS, Hammond KB, Accurso FJ, Sokol RJ. Prospective, long-term study of fat-soluble vitamin status in children with cystic fibrosis identified by newborn screen. J Pediatr 1999;135:601–10.
[114] Brei C, Simon A, Krawinkel MB, Naehrlich L. Individualized vitamin A supplementation for patients with cystic fibrosis. Clin Nutr 2013;32:805–10.
[115] Lancellotti L, D'Orazio C, Mastella G, Mazzi G, Lippi U. Deficiency of vitamins E and A in cystic fibrosis is independent of pancreatic function and current enzyme and vitamin supplementation. Eur J Pediatr 1996;155:281–5.
[116] Hakim F, Kerem E, Rivlin J, Bentur L, Stankiewicz H, Bdolach-Abram T, et al. Vitamins A and E and pulmonary exacerbations in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2007;45:347–53.
[117] Cameron C, Lodes MW, Gershan WM. Facial nerve palsy associated with a low serum vitamin A level in an infant with cystic fibrosis. J Cyst Fibros 2007;6:241–3.
[118] Ansari EA, Sahni K, Etherington C, Morton A, Conway SP, Moya E, et al. Ocular signs and symptoms and vitamin A status in patients with cystic fibrosis treated with daily vitamin A supplements. Br J Ophthalmol 1999;83:688–91.
[119] Scientific Committee on Food. Tolerable upper intake levels for vitamins and minerals. European Food Safety Authority; 2006.
[120] Lindblad A, Diczfalusy U, Hultcrantz R, Thorell A, Strandvik B. Vitamin A concentration in the liver decreases with age in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 1997;24:264–70.
[121] Maqbool A, Graham-Maar RC, Schall JI, Zemel BS, Stallings VA. Vitamin A intake and elevated serum retinol levels in children and young adults with cystic fibrosis. J Cyst Fibros 2008;7:137–41.
[122] Rust P, Eichler I, Renner S, Elmadfa I. Long-term oral beta-carotene supplementation in patients with cystic fibrosis - effects on antioxidative status and pulmonary function. Ann Nutr Metab 2000;44:30–7.
[123] Shenkin A. Physiological function and deficiency states of vitamins. In: Sobotka L, editor. Basics in clinical nutrition. 4th ed. Prague: Galén; 2011. p. 145–53.
[124] 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;84:174–82.
[125] Myhre AM, Carlsen MH, Bohn SK, Wold HL, Laake P, Blomhoff R. Water-miscible, emulsified, and solid forms of retinol supplements are more toxic than oil-based preparations. Am J Clin Nutr 2003;78:1152–9.
[126] IOM (Institute of Medicine). Dietary reference intakes: vitamin A, K, iron, zinc, and other elements. Washington, DC: National Academies Press; 2001. p. 773.
[127] Smets KJ, Barlow T, Vanhaesebrouck P. Maternal vitamin A deficiency and neonatal microphthalmia: complications of biliopancreatic diversion? Eur J Pediatr 2006;165:502–4.
[128] Green D, Carson K, Leonard A, Davis JE, Rosenstein B, Zeitlin P, et al. Current treatment recommendations for correcting vitamin D deficiency in pediatric patients with cystic fibrosis are inadequate. J Pediatr 2008;153:554–9.
[129] Hall WB, Sparks AA, Aris RM. Vitamin d deficiency in cystic fibrosis. Int J Endocrinol 2010;2010:218691.
[130] Robberecht E, Vandewalle S, Wehlou C, Kaufman JM, De Schepper J. Sunlight is an important determinant of vitamin D serum concentrations in cystic fibrosis. Eur J Clin Nutr 2011;65:574–9.
[131] Tangpricha V, Kelly A, Stephenson A, Maguiness K, Enders J, Robinson KA, et al. An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the Cystic Fibrosis Foundation. J Clin Endocrinol Metab 2012;97:1082–93.
[132] EFSA panel on dietetic products nutrition and allergies. Scientific opinion on the tolerable upper intake level of vitamin D. EFSA J 2012;10. 2813, 45pp.
[133] Braegger C, Campoy C, Colomb V, Decsi T, Domellof M, Fewtrell M, et al. Vitamin D in the healthy European paediatric population. J Pediatr Gastroenterol Nutr 2013;56:692–701.
[134] IOM (Institute of Medicine). Dietary reference intakes for calcium and vitamin D. Washington, D.C.: The National Academies Press; 2011.
[135] Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. Am J Clin Nutr 2012;95:1357–64.
[136] Shepherd D, Belessis Y, Katz T, Morton J, Field P, Jaffe A. Single high-dose oral vitamin D(3) (stoss) therapy – a solution to vitamin D deficiency in children with cystic fibrosis? J Cyst Fibros 2013;12:177–82.

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[137] Mailhot G. Vitamin D bioavailability in cystic fibrosis: a cause for concern? Nutr Rev 2012;70:280–93.
[138] Lagrange-Puget M, Durieu I, Ecochard R, Abbas-Chorfa F, Drai J, Steghens JP, et al. Longitudinal study of oxidative status in 312 cystic fibrosis patients in stable state and during bronchial exacerbation. Pediatr Pulmonol 2004;38:43–9.
[139] Cantin AM, Bilodeau G, Ouellet C, Liao J, Hanrahan JW. Oxidant stress suppresses CFTR expression. Am J Physiol Cell Physiol 2006;290:C262–70.
[140] Huang SH, Schall JI, Zemel BS, Stallings VA. Vitamin E status in children with cystic fibrosis and pancreatic insufficiency. J Pediatr 2006;148:556–9.
[141] Winklhofer-Roob BM, van't Hof MA, Shmerling DH. Long-term oral vitamin E supplementation in cystic fibrosis patients: RRR-alpha-tocopherol compared with all-rac-alpha-tocopheryl acetate preparations. Am J Clin Nutr 1996;63:722–8.
[142] Rhodes B, Nash EF, Tullis E, Pencharz PB, Brotherwood M, Dupuis A, et al. Prevalence of dyslipidemia in adults with cystic fibrosis. J Cyst Fibros 2010;9:24–8.
[143] Nast D, Paniagua C, Anderson P. Cystic fibrosis: a clinician's tool for management of care advancing into the adult population. J Am Acad Nurse Pract 2012;24:625–32.
[144] Dougherty KA, Schall JI, Stallings VA. Suboptimal vitamin K status despite supplementation in children and young adults with cystic fibrosis. Am J Clin Nutr 2010;92:660–7.
[145] Rashid M, Durie P, Andrew M, Kalnins D, Shin J, Corey M, et al. Prevalence of vitamin K deficiency in cystic fibrosis. Am J Clin Nutr 1999;70:378–82.
[146] Conway SP, Wolfe SP, Brownlee KG, White H, Oldroyd B, Truscott JG, et al. Vitamin K status among children with cystic fibrosis and its relationship to bone mineral density and bone turnover. Pediatrics 2005;115:1325–31.
[147] Drury D, Grey VL, Ferland G, Gundberg C, Lands LC. Efficacy of high dose phylloquinone in correcting vitamin K deficiency in cystic fibrosis. J Cyst Fibros 2008;7:457–9.
[148] Jagannath VA, Fedorowicz Z, Thaker V, Chang AB. Vitamin K supplementation for cystic fibrosis. Cochrane Database Syst Rev 2011:CD008482.
[149] Borowitz D, Konstan MW, O'Rourke A, Cohen M, Hendeles L, Murray FT. Coefficients of fat and nitrogen absorption in healthy subjects and individuals with cystic fibrosis. J Pediatr Pharmacol Ther 2007;12:47–52.
[150] Giuliano CA, Dehoorne-Smith ML, Kale-Pradhan PB. Pancreatic enzyme products: digesting the changes. Ann Pharmacother 2011;45:658–66.
[151] Trapnell BC, Maguiness K, Graff GR, Boyd D, Beckmann K, Caras S. Efficacy and safety of Creon 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2009;8:370–7.
[152] Wier HA, Kuhn RJ. Pancreatic enzyme supplementation. Curr Opin Pediatr 2011;23:541–4.
[153] Wooldridge JL, Heubi JE, Amaro-Galvez R, Boas SR, Blake KV, Nasr SZ, et al. EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency. J Cyst Fibros 2009;8:405–17.
[154] Haupt ME, Kwasny MJ, Schechter MS, McColley SA. Pancreatic enzyme replacement therapy dosing and nutritional outcomes in children with cystic fibrosis. J Pediatr 2014;164. 1110–1115 e1111.
[155] Dominguez-Munoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. Curr Gastroenterol Rep 2007;9:116–22.
[156] Brady MS, Garson JL, Krug SK, Kaul A, Rickard KA, Caffrey HH, et al. An enteric-coated high-buffered pancrelipase reduces steatorrhea in patients with cystic fibrosis: a prospective, randomized study. J Am Diet Assoc 2006;106:1181–6.
[157] Colombo C, Fredella C, Russo MC, Faelli N, Motta V, Valmarana L, et al. Efficacy and tolerability of Creon for Children in infants and toddlers with pancreatic exocrine insufficiency caused by cystic fibrosis: an open-label, single-arm, multicenter study. Pancreas 2009;38:693–9.
[158] Kashirskaya NY, Kapranov NI, Sander-Struckmeier S, Kovalev V. Safety and efficacy of Creon(R) Micro in children with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2014;14:275–81.
[159] Munck A, Duhamel JF, Lamireau T, Le Luyer B, Le Tallec C, Bellon G, et al. Pancreatic enzyme replacement therapy for young cystic fibrosis patients. J Cyst Fibros 2009;8:14–8.
[160] Graff GR, Maguiness K, McNamara J, Morton R, Boyd D, Beckmann K, et al. Efficacy and tolerability of a new formulation of pancrelipase delayed-release capsules in children aged 7 to 11 years with exocrine pancreatic insufficiency and cystic fibrosis: a multicenter, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. Clin Ther 2010;32:89–103.
[161] Graff GR, McNamara J, Royall J, Caras S, Forssmann K. Safety and tolerability of a new formulation of pancrelipase delayed-release capsules (CREON) in children under seven years of age with exocrine pancreatic insufficiency due to cystic fibrosis: an open-label, multicentre, single-treatment-arm study. Clin Drug Investig 2010;30:351–64.
[162] Maqbool A, Schall JI, Garcia-Espana JF, Zemel BS, Strandvik B, Stallings VA. Serum linoleic acid status as a clinical indicator of essential fatty acid status in children with cystic fibrosis. J Pediatr Gastroenterol Nutr 2008;47:635–44.
[163] Steinkamp G, Demmelmair H, Ruhl-Bagheri I, von der Hardt H, Koletzko B. Energy supplements rich in linoleic acid improve body weight and essential fatty acid status of cystic fibrosis patients. J Pediatr Gastroenterol Nutr 2000;31:418–23.
[164] van Egmond AW, Kosorok MR, Koscik R, Laxova A, Farrell PM. Effect of linoleic acid intake on growth of infants with cystic fibrosis. Am J Clin Nutr 1996;63:746–52.
[165] Conway S, Morton A, Wolfe S. Enteral tube feeding for cystic fibrosis. Cochrane Database Syst Rev 2012;12:CD001198.
[166] Olsen EM, Petersen J, Skovgaard AM, Weile B, Jorgensen T, Wright CM. Failure to thrive: the prevalence and concurrence of anthropometric criteria in a general infant population. Arch Dis Child 2007;92:109–14.
[167] Lai HJ, Shoff SM. Classification of malnutrition in cystic fibrosis: implications for evaluating and benchmarking clinical practice performance. Am J Clin Nutr 2008;88:161–6.
[168] Kindstedt-Arfwidson K, Strandvik B. Food intake in patients with cystic fibrosis on an ordinary diet. Scand J Gastroenterol Suppl 1988;143:160–2.
[169] Roulet M, Frascarolo P, Rappaz I, Pilet M. Essential fatty acid deficiency in well nourished young cystic fibrosis patients. Eur J Pediatr 1997;156:952–6.
[170] Jelalian E, Stark LJ, Reynolds L, Seifer R. Nutrition intervention for weight gain in cystic fibrosis: a meta analysis. J Pediatr 1998;132:486–92.
[171] Powers SW, Mitchell MJ, Patton SR, Byars KC, Jelalian E, Mulvihill MM, et al. Mealtime behaviors in families of infants and toddlers with cystic fibrosis. J Cyst Fibros 2005;4:175–82.
[172] Stark LJ, Quittner AL, Powers SW, Opipari-Arrigan L, Bean JA, Duggan C, et al. Randomized clinical trial of behavioral intervention and nutrition education to improve caloric intake and weight in children with cystic fibrosis. Arch Pediatr Adolesc Med 2009;163:915–21.
[173] Stark LJ, Opipari-Arrigan L, Quittner AL, Bean J, Powers SW. The effects of an intensive behavior and nutrition intervention compared to standard of care on weight outcomes in CF. Pediatr Pulmonol 2011;46:31–5.
[174] Abbott J, Morton AM, Musson H, Conway SP, Etherington C, Gee L, et al. Nutritional status, perceived body image and eating behaviours in adults with cystic fibrosis. Clin Nutr 2007;26:91–9.
[175] Shearer JE, Bryon M. The nature and prevalence of eating disorders and eating disturbance in adolescents with cystic fibrosis. J R Soc Med 2004;97(Suppl. 44):36–42.
[176] Gunnell S, Christensen NK, McDonald C, Jackson D. Attitudes toward percutaneous endoscopic gastrostomy placement in cystic fibrosis patients. J Pediatr Gastroenterol Nutr 2005;40:334–8.
[177] Rettammel AL, Marcus MS, Farrell PM, Sondel SA, Koscik RE, Mischler EH. Oral supplementation with a high-fat, high-energy product improves nutritional status and alters serum lipids in patients with cystic fibrosis. J Am Diet Assoc 1995;95:454–9.
[178] Shepherd RW, Holt TL, Cleghorn G, Ward LC, Isles A, Francis P. Short-term nutritional supplementation during management of pulmonary exacerbations in cystic fibrosis: a controlled study, including effects of protein turnover. Am J Clin Nutr 1988;48:235–9.
[179] Caramia G, Cocchi M, Gagliardini R, Malavolta M, Mozzon M, Frega NG. Fatty acids composition of plasma phospholipids and triglycerides in children with cystic fibrosis. The effect of dietary supplementation with an olive and soybean oils mixture. Pediatr Med Chir 2003;25:42–9.
[180] Olveira G, Olveira C, Acosta E, Espildora F, Garrido-Sanchez L, Garcia-Escobar E, et al. Fatty acid supplements improve respiratory, inflammatory and nutritional parameters in adults with cystic fibrosis. Arch Bronconeumol 2010;46:70–7.
[181] Best C, Brearley A, Gaillard P, Regelmann W, Billings J, Dunitz J, et al. A pre-post retrospective study of patients with cystic fibrosis and gastrostomy tubes. J Pediatr Gastroenterol Nutr 2011;53:453–8.
[182] Bradley GM, Blackman SM, Watson CP, Doshi VK, Cutting GR. Genetic modifiers of nutritional status in cystic fibrosis. Am J Clin Nutr 2012;96:1299–308.
[183] Efrati O, Mei-Zahav M, Rivlin J, Kerem E, Blau H, Barak A, et al. Long term nutritional rehabilitation by gastrostomy in Israeli patients with cystic fibrosis: clinical outcome in advanced pulmonary disease. J Pediatr Gastroenterol Nutr 2006;42:222–8.
[184] Steinkamp G, von der Hardt H. Improvement of nutritional status and lung function after long-term nocturnal gastrostomy feedings in cystic fibrosis. J Pediatr 1994;124:244–9.
[185] Truby H, Cowlishaw P, O'Neil C, Wainwright C. The long term efficacy of gastrostomy feeding in children with cystic fibrosis on anthropometric markers of nutritonal status and pulmonary function. Open Respir Med J 2009;3:112–5.
[186] Van Biervliet S, De Waele K, Van Winckel M, Robberecht E. Percutaneous endoscopic gastrostomy in cystic fibrosis: patient acceptance and effect of overnight tube feeding on nutritional status. Acta Gastroenterol Belg 2004;67:241–4.
[187] Walker SA, Gozal D. Pulmonary function correlates in the prediction of long-term weight gain in cystic fibrosis patients with gastrostomy tube feedings. J Pediatr Gastroenterol Nutr 1998;27:53–6.
[188] Houwen RH, van der Doef HP, Sermet I, Munck A, Hauser B, Walkowiak J, et al. Defining DIOS and constipation in cystic fibrosis with a multicentre study on the incidence, characteristics, and treatment of DIOS. J Pediatr Gastroenterol Nutr 2010;50:38–42.
[189] Colombo C, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M, et al. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. J Cyst Fibros 2011;10(Suppl. 2):S24–8.

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[190] Haworth CS. Impact of cystic fibrosis on bone health. Curr Opin Pulm Med 2010;16:616–22.
[191] Buntain HM, Schluter PJ, Bell SC, Greer RM, Wong JC, Batch J, et al. Controlled longitudinal study of bone mass accrual in children and adolescents with cystic fibrosis. Thorax 2006;61:146–54.
[192] Lucidi V, Bizzarri C, Alghisi F, Bella S, Russo B, Ubertini G, et al. Bone and body composition analyzed by Dual-energy X-ray Absorptiometry (DXA) in clinical and nutritional evaluation of young patients with Cystic Fibrosis: a cross-sectional study. BMC Pediatr 2009;9:61.
[193] Gronowitz E, Pitkanen S, Kjellmer I, Heikinheimo M, Strandvik B. Association between serum oncofetal antigens CA 19-9 and CA 125 and clinical status in patients with cystic fibrosis. Acta Paediatr 2003;92:1267–71.
[194] Gronowitz E, Lorentzon M, Ohlsson C, Mellstrom D, Strandvik B. Docosahexaenoic acid is associated with endosteal circumference in long bones in young males with cystic fibrosis. Br J Nutr 2008;99:160–7.
[195] Gronowitz E, Mellstrom D, Strandvik B. Serum phospholipid fatty acid pattern is associated with bone mineral density in children, but not adults, with cystic fibrosis. Br J Nutr 2006;95:1159–65.
[196] Conway SP, Oldroyd B, Brownlee KG, Wolfe SP, Truscott JG. A cross-sectional study of bone mineral density in children and adolescents attending a Cystic Fibrosis Centre. J Cyst Fibros 2008;7:469–76.
[197] Gronowitz E, Garemo M, Lindblad A, Mellstrom D, Strandvik B. Decreased bone mineral density in normal-growing patients with cystic fibrosis. Acta Paediatr 2003;92:688–93.
[198] Fewtrell MS, Benden C, Williams JE, Chomtho S, Ginty F, Nigdikar SV, et al. Undercarboxylated osteocalcin and bone mass in 8-12 year old children with cystic fibrosis. J Cyst Fibros 2008;7:307–12.
[199] Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care 2009;32:1626–31.
[200] Moran A, Pillay K, Becker DJ, Acerini CL. Management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes 2014;15(Suppl. 20):65–76.
[201] Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care 2010;33:2697–708.
[202] Colombo C, Battezzati PM, Crosignani A, Morabito A, Costantini D, Padoan R, et al. Liver disease in cystic fibrosis: a prospective study on incidence, risk factors, and outcome. Hepatology 2002;36:1374–82.
[203] Van Biervliet S, Van Biervliet JP, Robberecht E, Christophe A. Fatty acid composition of serum phospholipids in cystic fibrosis (CF) patients with or without CF related liver disease. Clin Chem Lab Med 2010;48:1751–5.
[204] Colombo C, Costantini D, Rocchi A, Romano G, Rossi G, Bianchi ML, et al. Effects of liver transplantation on the nutritional status of patients with cystic fibrosis. Transpl Int 2005;18:246–55.
[205] Christophe A, Robberecht E. Current knowledge on fatty acids in cystic fibrosis. Prostagl Leukot Essent Fat Acids 1996;55:129–38.
[206] Freedman SD, Blanco PG, Zaman MM, Shea JC, Ollero M, Hopper IK, et al. Association of cystic fibrosis with abnormalities in fatty acid metabolism. N Engl J Med 2004;350:560–9.
[207] Strandvik B, Gronowitz E, Enlund F, Martinsson T, Wahlstrom J. Essential fatty acid deficiency in relation to genotype in patients with cystic fibrosis. J Pediatr 2001;139:650–5.
[208] Carlstedt-Duke J, Bronnegard M, Strandvik B. Pathological regulation of arachidonic acid release in cystic fibrosis: the putative basic defect. Proc Natl Acad Sci U. S. A 1986;83:9202–6.
[209] Kuo PT, Huang NN, Bassett DR. The fatty acid composition of the serum chylomicrons and adipose tissue of children with cystic fibrosis of the pancreas. J Pediatr 1962;60:394–403.
[210] Coste TC, Armand M, Lebacq J, Lebecque P, Wallemacq P, Leal T. An overview of monitoring and supplementation of omega 3 fatty acids in cystic fibrosis. Clin Biochem 2007;40:511–20.
[211] Jorgensen MH, Ott P, Michaelsen KF, Porsgaard T, Jensen F, Lanng S. Long-chain PUFA in granulocytes, mononuclear cells, and RBC in patients with cystic fibrosis: relation to liver disease. J Pediatr Gastroenterol Nutr 2012;55:76–81.
[212] Njoroge SW, Seegmiller AC, Katrangi W, Laposata M. Increased Delta5- and Delta6-desaturase, cyclooxygenase-2, and lipoxygenase-5 expression and activity are associated with fatty acid and eicosanoid changes in cystic fibrosis. Biochim Biophys Acta 2011;1811:431–40.
[213] Wouthuyzen-Bakker M, Bodewes FA, Verkade HJ. Persistent fat malabsorption in cystic fibrosis; lessons from patients and mice. J Cyst Fibros 2011;10:150–8.
[214] Lloyd-Still JD, Bibus DM, Powers CA, Johnson SB, Holman RT. Essential fatty acid deficiency and predisposition to lung disease in cystic fibrosis. Acta Paediatr 1996;85:1426–32.
[215] Walkowiak J, Lisowska A, Blaszczynski M, Przyslawski J, Walczak M. Polyunsaturated fatty acids in cystic fibrosis are related to nutrition and clinical expression of the disease. J Pediatr Gastroenterol Nutr 2007;45:488–9. author reply 489.
[216] Panchaud A, Sauty A, Kernen Y, Decosterd LA, Buclin T, Boulat O, et al. Biological effects of a dietary omega-3 polyunsaturated fatty acids supplementation in cystic fibrosis patients: a randomized, crossover placebo-controlled trial. Clin Nutr 2006;25:418–27.
[217] Strandvik B, Berg U, Kallner A, Kusoffsky E. Effect on renal function of essential fatty acid supplementation in cystic fibrosis. J Pediatr 1989;115:242–50.
[218] Alicandro G, Faelli N, Gagliardini R, Santini B, Magazzu G, Biffi A, et al. A randomized placebo-controlled study on high-dose oral algal docosahexaenoic acid supplementation in children with cystic fibrosis. Prostagl Leukot Essent Fat Acids 2013;88:163–9.
[219] De Vizia B, Raia V, Spano C, Pavlidis C, Coruzzo A, Alessio M. Effect of an 8-month treatment with omega-3 fatty acids (eicosapentaenoic and docosahexaenoic) in patients with cystic fibrosis. JPEN J Parenter Enteral Nutr 2003;27:52–7.
[220] Keen C, Olin AC, Eriksson S, Ekman A, Lindblad A, Basu S, et al. Supplementation with fatty acids influences the airway nitric oxide and inflammatory markers in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2010;50:537–44.
[221] Oliver C, Watson H. Omega-3 fatty acids for cystic fibrosis. Cochrane Database Syst Rev 2013;11:CD002201.
[222] Bianchi ML, Colombo C, Assael BM, Dubini A, Lombardo M, Quattrucci S, et al. Treatment of low bone density in young people with cystic fibrosis: a multicentre, prospective, open-label observational study of calcium and calcifediol followed by a randomised placebo-controlled trial of alendronate. Lancet Respir Med 2013;1:377–85.
[223] Stalvey MS, Clines GA. Cystic fibrosis-related bone disease: insights into a growing problem. Curr Opin Endocrinol Diabetes Obes 2013;20:547–52.
[224] Whyte MP, McAlister WH, Novack DV, Clements KL, Schoenecker PL, Wenkert D. Bisphosphonate-induced osteopetrosis: novel bone modeling defects, metaphyseal osteopenia, and osteosclerosis fractures after drug exposure ceases. J Bone Min Res 2008;23:1698–707.
[225] Hardin DS. A review of the management of two common clinical problems found in patients with cystic fibrosis: cystic fibrosis-related diabetes and poor growth. Horm Res 2007;68(Suppl. 5):113–6.
[226] Bianchi ML, Romano G, Saraifoger S, Costantini D, Limonta C, Colombo C. BMD and body composition in children and young patients affected by cystic fibrosis. J Bone Min Res 2006;21:388–96.
[227] Phung OJ, Coleman CI, Baker EL, Scholle JM, Girotto JE, Makanji SS, et al. Recombinant human growth hormone in the treatment of patients with cystic fibrosis. Pediatrics 2010;126:e1211–26.
[228] Stalvey MS, Anbar RD, Konstan MW, Jacobs JR, Bakker B, Lippe B, et al. A multi-center controlled trial of growth hormone treatment in children with cystic fibrosis. Pediatr Pulmonol 2012;47:252–63.
[229] Thaker V, Haagensen AL, Carter B, Fedorowicz Z, Houston BW. Recombinant growth hormone therapy for cystic fibrosis in children and young adults. Cochrane Database Syst Rev 2013;6:CD008901.
[230] Marchand V, Baker SS, Stark TJ, Baker RD. Randomized, double-blind, placebo-controlled pilot trial of megestrol acetate in malnourished children with cystic fibrosis. J Pediatr Gastroenterol Nutr 2000;31:264–9.
[231] Eubanks V, Koppersmith N, Wooldridge N, Clancy JP, Lyrene R, Arani RB, et al. Effects of megestrol acetate on weight gain, body composition, and pulmonary function in patients with cystic fibrosis. J Pediatr 2002;140:439–44.
[232] Homnick DN, Homnick BD, Reeves AJ, Marks JH, Pimentel RS, Bonnema SK. Cyproheptadine is an effective appetite stimulant in cystic fibrosis. Pediatr Pulmonol 2004;38:129–34.
[233] Epifanio M, Marostica PC, Mattiello R, Feix L, Nejedlo R, Fischer GB, et al. A randomized, double-blind, placebo-controlled trial of cyproheptadine for appetite stimulation in cystic fibrosis. J Pediatr (Rio J) 2012;88:155–60.
[234] Butel MJ. Probiotics, gut microbiota and health. Med Mal Infect 2014;44:1–8.
[235] Chiu YH, Lin SL, Tsai JJ, Lin MY. Probiotic actions on diseases: implications for therapeutic treatments. Food Funct 2014;5:625–34.
[236] Bruzzese E, Raia V, Gaudiello G, Polito G, Buccigrossi V, Formicola V, et al. Intestinal inflammation is a frequent feature of cystic fibrosis and is reduced by probiotic administration. Aliment Pharmacol Ther 2004;20:813–9.
[237] Bruzzese E, Raia V, Spagnuolo MI, Volpicelli M, De Marco G, Maiuri L, et al. Effect of Lactobacillus GG supplementation on pulmonary exacerbations in patients with cystic fibrosis: a pilot study. Clin Nutr 2007;26:322–8.
[238] Weiss B, Bujanover Y, Yahav Y, Vilozni D, Fireman E, Efrati O. Probiotic supplementation affects pulmonary exacerbations in patients with cystic fibrosis: a pilot study. Pediatr Pulmonol 2010;45:536–40.
[239] Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. Science 1989;245:1073–80.
[240] Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989;245:1066–73.

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