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Consensus Report

Nutrition in patients with cystic fibrosis: a European Consensus☆

M. Sinaasappel[a,*], M. Stern[b], J. Littlewood[c], S. Wolfe[c], G. Steinkamp[d], Harry G.M. Heijerman[e], E. Robberecht[f], G. Döring[g]

[a]*Department of Paediatric Gastroenterology, Erasmus Medical Centre, Rotterdam, The Netherlands*
[b]*Department of Paediatrics, University of Tübingen, Tübingen, Germany*
[c]*Regional Paediatric Cystic Fibrosis Unit, St James University Hospital, Leeds, UK*
[d]*Department of Paediatrics and Paediatric Pulmonology, Medizinische Hochschule, Hannover, Germany*
[e]*Ziekenhuis Leyenburg, The Hague, The Netherlands*
[f]*Department of Paediatrics, University of Ghent, Ghent, Belgium*
[g]*Hygiene-institut University of Tübingen, Tübingen, Germany*

Abstract

This document is the result of an European Consensus conference which took place in Artimino, Tuscany, Italy, in March 2001 involving 33 experts on nutrition in patients with cystic fibrosis, organised by the European Cystic Fibrosis Society, and sponsored by Axcan-Scandipharm, Baxter, Dr Falk Pharma, Fresenius, Nutricia, SHS International, Solvay Pharmaceuticals (major sponsor). The purpose of the conference was to develop a consensus document on nutrition in patients with cystic fibrosis based on current evidence. © 2002 European Cystic Fibrosis Society. Published by Elsevier Science B.V. All rights reserved.

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*Corresponding author.

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1. Introduction

Cystic fibrosis (CF) is a world-wide disease occurring in virtually all ethnic groups. In Caucasians it is the most common lethal hereditary disorder with autosomal recessive inheritance [1]. Approximately 1 in 25 are heterozygous carriers, while the incidence of clinical disease is approximately 1 in 2500 live births [1]. The condition is caused by mutations in a single gene of chromosome 7, which encodes the CF transmembrane conductance regulator (CFTR) [2]. The CFTR protein is a membrane bound cAMP-regulated chloride channel, which is thought to regulate other cell membrane ion channels [3]. More than 1000 different mutations have been identified so far; however, a deletion of phenylalanine in the amino acid position 508 is present in approximately 66% of chromosomes of all patients with CF world-wide.

CFTR mutations affect epithelial ion and water transport mainly in cells in the respiratory, gastrointestinal, hepatobiliary, reproductive tracts and sweat glands. The lack of chloride secretion in the pancreatic duct is responsible for obstruction and autodigestion of the pancreas early in embryonic life leading to severe exocrine pancreatic insufficiency in approximately 85% of CF newborns. In addition, intestinal obstruction complicates the neonatal period in 10–15% of the infants. Both inadequately treated pancreatic insufficiency and intestinal obstruction were held responsible for a high morbidity and mortality rate in patients with CF before 1970. As a result of various factors including better neonatal care, surgery, antibiotic treatment of pulmonary complications and improved nutrition, the median survival time of the patients has increased over the last three decades from 10 to 30 years. Nevertheless, it is still not clear to what extent improved nutritional status contributes to increased survival. In a recent report wasting was shown to be a significant predictor of survival in patients with CF independent of lung function, arterial blood oxygen and carbon dioxide tensions [4]. The fact that there is a remarkably close relationship between body weight and lung function and that terminal patients with CF are almost always severely malnourished, suggests that good nutritional care is of benefit for the patient with cystic fibrosis.

2. Nutritional deficiencies in CF

2.1. Nutrition and growth of individuals with CF

2.1.1. Growth during infancy

The mean birth weight of CF populations has been reported as subnormal (CF males: 3.18 kg, females: 3.04 kg; unaffected males: 3.37 kg, females: 3.25 kg) [5]. However, others have failed to confirm the finding of lower birth weights in CF [6,7].

Another study found children with CF to have a reduced length (-1.24 standard deviation, S.D.) weight (-0.72 S.D.) and head circumferences (-1.82 S.D.) compared with controls [8]. However, these data may not be representative since 34.6% of the infants were affected by meconium ileus, which is associated with worse outcomes [8].

The early growth pattern of infants with CF is dependent on both the age at diagnosis and the quality of the subsequent treatment they receive. The majority have pancreatic insufficiency and experience early gastrointestinal symptoms, which if not adequately treated can lead to subnormal weight gain. Even some infants diagnosed by neonatal screening have subnormal growth throughout the first year if the start of treatment is delayed by more than a few weeks after birth [9].

2.1.2. Growth after infancy

Subsequent growth velocity of CF infants is usually normal if chest infections are prevented or effectively treated and the intestinal malabsorption is adequately treated [6,7]. Almost normal growth and weight gain was maintained throughout childhood in Canadian patients with CF [10] and in 51 Swedish children with CF height gain was normal between 5 and 8 years [11]. The authors conclude that subnormal growth in infancy can be compensated for by catch-up growth thereafter. In Australian patients growth, weight and respiratory function were better at the age of 10 years in a group

of screened patients than in those born before screening was introduced [12].

As a consequence of patient registries, data from larger numbers of patients with CF are available for epidemiological investigations. In 1998 the Cystic Fibrosis Foundation (CFF) reported that 12.7% of children and 21.6% of adults were below 85% weight for height [13]. Comparable median centile values for Canadian and American patients with CF were: for height 28 and 21, respectively, weight 27 and 22, respectively, but both were 103% of ideal weight for height [14]. Data from the UK CF registry revealed that the mean weight S.D. scores of the males were between −0.25 and −0.5 until the age of 10 years after which they declined as did the body mass index (BMI). The mean weight S.D. scores of females were approximately −0.5 but they had a declining BMI after the age of 5 years [15,16]. After 10 years there was a progressive decline in SD scores for both height and weight. This deterioration in S.D. scores after the age of 10 years could be explained by some delay in the onset of puberty. However, it is more likely to be a reflection of an overall deterioration associated with an increase in the severity of the pulmonary disease.

It is increasingly apparent that the condition of the patients is closely related to the treatment they receive and that patients may be in a better nutritional state in clinics where regular attention is paid to nutrition and growth. It is encouraging that the nutritional state of new patients with CF has steadily improved over the years [17].

2.1.3. Delayed puberty and growth spurt

There is delay in the onset of puberty and menarche in patients with CF who have significant nutritional problems [18–20]; even in well-nourished females some delay has been reported [19]. Surprisingly the delay in skeletal maturation is modest in most patients with CF and seems to increase with age, as pulmonary problems become more severe [5].

3. Malnutrition: definition and assessment

3.1. Evaluation of nutrition and growth: anthropometry

3.1.1. Weight and height

The patient should see an experienced doctor at every visit and the specialist CF dietician at most clinic visits and always if weight progress is unsatisfactory [21,22]. Weight and height should be accurately measured at each clinic attendance by trained clinic staff [23]; these measurements should be charted to assess progress and compared to reference values [24–27]. Caution should be exercised when different anthropometric standards are compared [28]. Values are expressed either as (per) centiles, as percentage of the normal values for age or as standard deviation (S.D.) or *Z* scores. Percentage weight for height, weight for age and height for age are often used when expressing the nutritional status of children and are preferred to body mass index (BMI). The measurements are calculated from the standard equation:

$$\frac{\text{Current weight (kg)}}{\text{Weight (kg) equivalent to current height percentile}} \times 100$$

When considering S.D. scores, for a population whose values are normally distributed, the relationship of percentiles and S.D. scores are as follows: −2.0 S.D. (2.28th centile), 0 S.D. (50th centile), +2.0 S.D. (97.72nd centile) [24].

3.1.2. The body mass index (BMI)

The BMI (weight [kg]/height [m^2]) shows a reasonable correlation to body fat mass in adults, but less so in children, and is in the first place used to quantify obesity. Some adult CF clinics use BMI as a measure of nutritional state in their patients whose growth has ceased. Recently BMI categories for adults have been redefined as underweight (<18.5), ideal (18.5–24.9), pre-obese (25.0–29.9) and obese (≥30.0) [29]. In children BMI values must be interpreted on the basis of comparison with age and gender specific reference centiles [30] or S.D. scores. A low BMI without deficient fatness will be found in patients with proportionately long limbs and a short trunk, where there is poor musculature or in adolescents with delayed puberty [24]. In children and adolescents, no advantage has been shown of using BMI, rather than weight for height, for documenting malnutrition.

3.1.3. Other measurements

The mid upper arm circumference and skinfold measurements [31] are held inappropriate for the detailed monitoring required in CF [32]. Noting the stages of breast, pubic hair and genital development and recording the age of the menarche in girls are important as a measure of the stage of development [25] for the correct interpretation of changes in weight and height gain during adolescence. Thus, after the age of 10 years knowledge of the puberty state is required to adequately assess growth and nutrition. More sophisticated methods of measuring body composition, that are used primarily for research purposes, offer more accurate assessment of nutritional status and growth response to nutritional therapy. These methods include total body potassium [33,34], total body electrical conductivity, bioelectrical impedance analysis [35], total body water by isotope dilution and dual energy X-ray absorptiometry [36]. Osteopenia and osteoporosis have been described in both adults and children with CF [37,38]. Bone mineral

Table 1
Guidelines for nutritional intervention. In case of malnutrition or weight loss there should be a full re-evaluation of all possible causes that affect nutritional state. If nutritional intervention is indicated the following guidelines can be used. First enhance nutritional density/optimal intake before starting supplements

	<2 years	2–18 years	>18 years
Normal nutritional state Preventive counselling	% wt./ht 90–110	% wt./ht 90–110	BMI 18.5–25 or no recent wt. loss
Dietetic referral indicated Consider supplements	Any degree of failure to thrive	%wt./ht 85–89 or wt. loss over 4-6 months or plateau in wt over 6 months	BMI <18.5 or 5% wt. loss over <2 months
Invasive nutritional support	Failure to thrive despite oral supplementation	Supplements tried and either: %wt./ht <85 or wt. falling 2 centile positions	Supplements tried and either: BMI<18.5 or >5% wt. loss over <2 months

For all age categories pay special attention if stunting is evident as defined: (1) height centile <0.4th; (2) Ht/age <90%.

density (BMD) is best determined by dual energy X-ray absorptiometry (DEXA). DEXA scans, which can simultaneously assess fat mass and lean body mass, can be carried out in most major CF units, and should be considered as part of the nutritional assessment in all patients over the age of 10 years, but there is no documented evidence of the benefit of regular DEXA scans that are followed by targeted intervention.

3.1.4. Rate of weight gain and growth

The weight for height should remain above 90% and ideally should be over 95%. Oral energy supplements are usually advised if the weight for height is between 85 and 90% in children or the BMI is less than 18.5 in adults and enteral tube feeding if weight for height falls below 85% or BMI is less than 18.5, despite trying oral energy supplements (see Table 1). Other causes of abnormal nutrition and growth include either gastrointestinal disorders such as food intolerance, coeliac disease or inflammatory bowel disease [39] or even endocrine disorders [40]. Oral or long-term inhaled steroid therapy [41] may cause a slowing of height gain in the presence of apparently normal or excessive weight gain.

3.2. Laboratory investigations

A variety of investigations may be helpful in the assessment of the patient's nutritional state [42], such as haemoglobin, total white cell and neutrophil count, serum albumin and/or pre-albumin. Urea and electrolytes should be checked whenever clinical progress is not entirely satisfactory to identify salt depletion and pseudo-Bartter's syndrome, which may cause significant growth failure [43]. Besides an ultrasound examination of the liver and upper abdomen, plasma fat-soluble vitamin A, D and E levels should be measured annually.

3.3. Definition of malnutrition

Malnutrition is defined as a weight for height value below 90% in children or as BMI below 18.5 in adults.

4. Factors contributing to malnutrition in CF

4.1. Features of malabsorption in CF patients

Malabsorption is characterised by foul smelling loose pale stools. Infants identified through newborn screening exhibit intestinal malabsorption which is of early onset and severe and if left untreated leads to severe malnutrition and growth failure [44]. Newly diagnosed children and adults may have untreated malabsorption and should be evaluated. Due to the progressive nature of the pancreatic damage, pancreatic sufficient patients [45] may eventually develop pancreatic insufficiency [46]. Malabsorption of fat and nitrogen is severe without enzyme treatment; nonetheless, some 40–50% of ingested dietary fat is absorbed without treatment. This is probably due to the action of lingual and gastric lipase [47]. Carbohydrate malabsorption is minimal [48]. Even when clinical symptoms appear to be controlled by pancreatic enzyme supplementation, many patients still have a significant degree of fat malabsorption. Thus, the control of gastrointestinal signs and symptoms is not always indicative that malabsorption is controlled. Equally, persisting abdominal signs and symptoms in the face of apparently reasonable doses of enzymes may not be due to inadequate enzyme treatment but some other cause such as constipation [39].

4.1.1. Factors other than enzyme deficiency contributing to malabsorption

Deficiency of pancreatic enzymes is the most important, but not the only factor, responsible for malabsorption in CF [49]. A further important consequence of the severe pancreatic damage is deficiency of pancreatic bicarbonate resulting in diminished capacity to buffer influxes of gastric acid into the duodenum [50]. This results in reduced efficacy of endogenous and exogenous pancreatic enzymes and precipitation of bile salts [51,52]. Bile salt replacement contains a relative reduction in taurine-conjugated and an increase in glycine-conjugated bile salts [53], the latter being less effective

at lipid solubilisation. Mucosal ion transport abnormalities resulting from deficiency of intestinal CFTR affect both water and electrolyte transport [54]. In an acid medium fatty acids, which are formed by fat digestion at the oil/water interphase, are not converted into soaps but occur in the protonated form. In this form, they are not transferred to the micellar phase but remain in the oil phase. This may further hamper fat digestion as under these conditions pancreatic lipase may catalyse the formation of triglycerides out of their digestion products. There may also be impaired mucosal uptake and transport of long chain fatty acids [55] as well as altered motility with an increase in small bowel transit time [56]. A variety of structural abnormalities may result from previous gastrointestinal surgery for meconium ileus including shortened bowel, strictures at the site of previous intestinal anastomosis, malrotation and adhesions. In all patients there are histological abnormalities of the bowel wall characteristic of CF and an excess of mucus may also be relevant [57].

4.1.2. Investigation and diagnosis of malabsorption

It is important to obtain some objective evidence of both intestinal malabsorption and pancreatic abnormality in all patients with CF both to identify those who require enzyme treatment, and to monitor the success of such treatment. If there is abdominal distension, abdominal discomfort, loose oily pale stools, and the patient is malnourished it is most likely that there is intestinal malabsorption [39,58]. Demonstrating that intestinal absorption is controlled prevents unnecessary and potentially harmful increases in the enzyme dose and also prompts a search for another cause for the symptoms [22]. Poor weight gain and growth, particularly if the appetite is good, are suggestive of malabsorption. Indirect pancreatic function tests, which detect abnormalities secondary to loss of pancreatic function, such as maldigestion and consequent malabsorption, are generally employed, because they are easier to perform and less invasive than direct assessment of the secretory capacity of the exocrine pancreas

The degree of fat malabsorption is usually taken as the marker of intestinal malabsorption. The gold standard for measuring fat absorption is an assessment of the fat excretion over 3 days and its relation to dietary fat intake over the same time period. Normally the equivalent of less than 7% of the fat ingested is excreted i.e. there is over 93% fat absorption. The total faecal fat output is usually less than 7 g per day in healthy adults and less than 2 g in small children [59]. Measurement of faecal fat using near infrared spectroscopy [60] compares favourably with the routine titrimetric method [61]. As a minimum measurement of steatorrhoea, a semiquantitative estimate of faecal fat content should be made by a method of faecal microscopy or acid steatocrit, which have been validated by comparison with quantitative measurements [62,63]. Other indirect pancreatic function tests including the determination of relatively non-biodegradable pancreatic enzymes in faeces (chymotrypsin [64] and particularly, faecal pancreatic elastase 1 [65,66]) and tests which evaluate the capacity of pancreatic enzymes to cleave specific synthetic substrates (e.g. PABA). The ^{13}carbon mixed triglyceride breath test is a safe non-invasive way of assessing fat digestion that can be used repeatedly in children [67]. However, a large inter-individual variation under condition of relatively mild fat malabsorption has recently been documented in a rat model, suggesting that this test, as most other indirect tests of pancreatic function may be particularly useful for revealing severe pancreatic insufficiency [68]. The serum concentrations of specific pancreatic enzymes (immunoreactive trypsin [69] and lipase) can be used to document residual pancreatic function.

4.2. Energy expenditure

The main factors leading to energy loss are malabsorption due to pancreatic insufficiency and inflammation. Glucosuria in diabetic patients and protein loss in large amounts of sputum may contribute to energy losses. As the energy intake is often lower than the 120–150% of the recommended daily amount, a negative energy balance is frequently seen in patients with CF. Energy requirements are determined by measuring energy expenditure. Approximately 60–70% of total energy expenditure is determined by resting energy expenditure (REE), 10–25% by physical activity, and 10% for diet-induced thermogenesis.

Energy expenditure can either be measured or calculated. Methods for quantifying energy expenditure are: (1) indirect calorimetry; (2) direct calorimetry; (3) 24-h energy expenditure with stable isotopes; and (4) the 24-h monitoring of heart rate. Intra-individual variation of direct or indirect calorimetry is approximately 3%, while the 24-h techniques have much larger variances (10–15%). If techniques for measuring energy expenditure are unavailable; (5) REE can be estimated from body size. A direct comparison of these standards and measured values revealed differences of up to $\pm 20\%$ in healthy individuals. For patients with CF, a specific formula has been developed which is based on the FAO/WHO/UNO equation and supplemented with disease and activity factors [21]. However, when compared with results from indirect calorimetry, this equation underestimated REE in children and infants with CF [70,71].

Many investigators report on increased REE in patients with CF [72–78]. This increased REE is not always associated with an increase in total energy expenditure, especially in stable patients with moderate pulmonary disease [79]. With few exceptions, mean

REE was reported to be increased by 7–35% in patients with CF compared with predicted values. However, a large range of values was obtained between different individuals. Impaired lung function causes a higher workload for respiratory muscles, and increased oxygen cost of breathing, causing in CF a REE twice that of controls [72]. Chronic inflammation may also be associated with higher energy expenditure and correlations with concentrations of TNFα have been reported [77]. Acute respiratory exacerbations cause an increased REE in many patients, which reverts to lower values after antibiotic therapy [74–77]. Similarly, after 2 weeks of aerosolised dornase alpha, a decline of REE was observed [78]. Some authors reported correlations with improvements of FEV_1, CRP, TNFα, or body weight, suggesting a parallel reduction in the host inflammatory and catabolic responses after treatment.

Patients homozygous for ΔF_{508} were reported in some studies to have higher mean REE [80–82], whereas other authors did not find such a relation [83,84]. Therefore, if an energy-requiring defect is present in CF, its contribution to increased REE must be small. There is a paucity of data concerning longitudinal follow-up of individual patients. In the only long-term observational trial REE was considered as an early indicator of disease severity independent of pulmonary function [81].

Beta-agonists are bronchodilators that are frequently administered in patients with CF. Salbutamol, a major drug of this class, has been shown to increase resting energy expenditure by 10% during the first hour after inhalation [85]. When administering beta-agonists several times a day, an effect on energy requirements should be considered.

4.3. Inadequate energy intake

The poor energy intake of many individuals with CF has been well documented. Although intakes in excess of 120% of the estimated average requirement are commonly advised, when the actual energy intake is measured it is often considerably less than this [86], particularly in male patients [87].

Additionally, specific muscle stimulation with anabolic medication appears to be an option. In patients with CF it has been shown that megestrol acetate, a progestagon, leads to an increased appetite, an increase in bodyweight with an increase in lean body mass and pulmonary function [88–90]. Disadvantages are the possible development of diabetes, inhibition of growth and adrenal suppression [89]. This is a subject which need further research, and because of the side effects and the limited data available, patients should only be treated with anabolic medication in clinical trials. Growth hormone has also been shown to improve growth and clinical status in pre-pubertal patients with CF [91]. Growth hormone therapy is also associated with a number of side effect e.g. glucose intolerance. Further research is required before its use can be widely accepted in the clinical situation.

4.4. Liver disease and bile salt loss

A significant percentage of individuals with CF eventually have biochemical, ultrasound or clinical evidence of liver disease. Prevalence estimates of liver involvement in CF remain highly variable; ranging between 2% and 37% among the studies based on the largest CF series. On the other hand three prospective studies recently carried out indicate that liver disease is a relative frequent and early complication of CF. Prevalence of cirrhosis is approximately 10% [92,93]. In one third of these patients liver disease develops before the age of 5 years. Patients with CF who have overt clinical liver disease commonly have serious nutritional problems both generally and also relating to specific macronutrients, fat-soluble vitamins and clotting factors [94]. Many patients with CF have increased losses of bile salts in the intestine [52]. Bile salt deficiency compromises lipolysis leading to a reduction in fat absorption of up to 50%. In one study lipolysis of the substrate was not affected in patients with CF related liver disease using the ^{13}C-mixed triacylglycerol breath test [95], but, bile salt concentration or intestinal loss was not studied. Ursodeoxycholic acid (URSO) is accepted as a treatment for biochemical liver disease and has a beneficial effect on liver enzyme levels. Whether treatment with URSO leads to an improvement in nutritional state is unknown. Studies that show long-term effects on the prevention of fibrosis are lacking, and the observation that the nutritional state of patients with CF and liver disease improved with URSO [96] was not confirmed in a controlled trial [97]. Liver transplantation in such patients, however, has a beneficial effect on their nutritional state [98].

4.5. Diabetes mellitus

Estimates of prevalence of CF related diabetes mellitus (CFRD) vary from 2.5% to 12% of patients, increasing considerably with age. In Denmark, 32% of patients with CF developed diabetes mellitus by the age of 25 years [99]. This obviously has considerable nutritional significance. CF related diabetes mellitus shares features of both type 1 and type 2 diabetes but is a distinct clinical entity. The primary cause is insulin deficiency but it is also influenced by unique CF conditions. Undernutrition, chronic and acute infection, elevated energy expenditure, glucagon deficiency, malabsorption, abnormal intestinal transit time, bacterial overgrowth, and liver dysfunction all influence glucose tolerance.

The diagnostic criteria of (CFRD) are reported in a recent consensus report of the US CF Foundation [100]:

(i) 2-h plasma glucose (PG) >11 mmol/l during a 75-g OGTT; (ii) fasting PG (FPG) >7.0 mmol/l on two or more occasions; (iii) FPG >7.0 mmol/l plus casual glucose level >11.1 mmol/l regardless time or last meal; and (iv) casual glucose levels >11.1 mmol/l on two or more occasions with symptoms. The HbA1c screening should not be used for detection of new cases of CF related diabetes mellitus but only for monitoring the degree of control of blood glucose levels in patients with established CFRD. The management of CFRD is beyond the scope of the present consensus on nutrition.

5. Essential fatty acid (EFA) deficiency

Patients with CF carry a high risk of low essential fatty acid levels, which have often been considered as essential fatty acid deficiency. Plasma and tissue lipids of patients with CF tend to have low contents of the precursor EFA, linoleic and α-linolenic acids [101,102]. Several studies have also reported reduced levels of omega-3 long-chain polyunsaturated fatty acids (LC-PUFA), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [103]. In contrast, controversial data exist for omega-6 LC-PUFA, such as arachidonic acid (AA), which may be normal, reduced or even increased [103]. A disturbed EFA and LC-PUFA status has been related to a variety of physiological impairments and adverse effects, such as altered membrane and cellular functions, skin lesions, alteration of immune, renal, hepatic and pulmonary functions [104,105]. Many of these symptoms are also observed in animals with experimental EFA deficiency [106]. However, the question of possible causality in patients with CF requires further clarification.

Proposed mechanisms that can lead to polyunsaturated fatty acid depletion in patients with CF include maldigestion and malabsorption of dietary lipids, as well as underweight and negative energy balance with an increased beta-oxidation of polyunsaturated fatty acids. Moreover, enhanced peroxidative destruction of polyunsaturated fatty acids in patients with poor antioxidant status and high oxidative stress induced by infections may contribute to low polyunsaturated fatty acid concentrations. Alterations of EFA conversion to LC-PUFA which were proposed to be either causally linked to the basic defect in CF or secondary to disease related physiological alterations, an increased turnover of linoleic acid [107] and an increased release of arachidonic acid (AA) from phospholipids [108] have been proposed but require further clarification. It is also of interest that in a controlled trial, URSO therapy for 6 months led to an improvement of the EFA status [109].

6. Vitamin deficiency

6.1. Vitamin A

Low serum vitamin A concentrations are frequent in untreated patients with CF, regardless of age, nutritional status, meconium ileus, Shwachman score, genotype and exocrine pancreatic function [110]. Pancreatic enzyme replacement to correct steatorrhoea apparently fails to normalise serum vitamin A concentrations. The occurrence of biochemical deficiency in patients without steatorrhoea, suggests that other mechanisms, such as a disturbance in mobilisation of hepatic stores, are involved. A positive correlation between retinol binding protein (RBP) concentrations and zinc status has been demonstrated [111]. Studies currently available trying to clarify the interrelationship between vitamin A status and liver disease are inconclusive. In a recent study hepatic vitamin A stores in CF were found to be lower than normal, they decreased with age and showed no correlation to the severity of CF related liver disease [112].

Many studies of vitamin A in CF underline the poor correlation between biochemical and clinical findings. However, patients with CF with decreased serum retinol concentrations were found to have disturbed dark adaptation, which was reversed by supplementing vitamin A [113]. Morphological changes of the eye like xerosis, have been reported recently but are exceptional [114]. Low vitamin A levels are associated with poorer clinical status [115] and impaired lung function [116]. Whether this is related to the role of vitamin A in the immune system or any other specific function is unclear. Plasma levels of β-carotene that acts as an antioxidant on its own are low in practically all pancreatic insufficient patients with CF.

6.2. Vitamin D

A quarter of infants with CF detected in a newborn screening program were shown to have decreased serum concentrations of 25-OH-cholecalciferol in the first 3 months of life, before any treatment was started [117]. This finding could be explained by the low serum levels of the vitamin D-binding protein in CF homozygotes, suggesting that in CF hypovitaminosis D is mainly a transport problem [118]. Sunlight is the major determinant of the amount of vitamin D in the body, which mainly depends on seasonal variation, geographical location and skin pigmentation. When there is sufficient skin exposure to ultraviolet light, dietary supplementation is not essential. As result it is very difficult to establish normal serum values and the frequency of deficiency in different studies varies accordingly [119]. For vitamin D decreased biochemical concentrations have also been found much more frequently than clinical

deficiency states such as rickets. In adolescents and adults osteopenia and osteoporosis are well documented but decreased vitamin D concentrations only play a minor part [119,120].

There are anecdotal reports of severe clinical deficiency states in heavily pigmented adolescents living in northern regions, after darker winter months.

6.3. Vitamin E

α-Tocopherol is a powerful antioxidant protecting lipoproteins and cellular membranes against destruction. Oxidative stress is enhanced in patients with CF due to chronic respiratory inflammation [121]. Almost all newly diagnosed patients with CF have low vitamin E plasma concentrations irrespective of exocrine pancreatic function [110]. This and the fact that administration of pancreatic enzymes does not correct an existing biochemical vitamin E deficiency suggests that exocrine pancreatic insufficiency is not the only underlying pathogenetic mechanism. Impaired intestinal availability of bile acids plays an equal or even more important role in vitamin E uptake from the gut [122,123]. CF related liver disease with only mild cholestasis does not seem to play a significant role in this context [124]. Vitamin E absorption is also improved by URSO [124]

Although biochemical vitamin E deficiency is a frequent finding in patients with CF, clinical symptoms are a rare event. However, long-standing severe biochemical deficiency will eventually result in irreversible neurological damage. Therefore, routine testing for biochemical vitamin E deficiency is recommended. A consequence of biochemical vitamin E deficiency is an impairment of the resistance of plasma lipids to oxidation [125]. In infants with CF, clinical deficiency mainly presents as haemolytic anaemia while in older patients symptoms are related to the nervous system [126,127]. In one study abnormal brainstem evoked auditory potentials were detected and proposed as useful in the evaluation [128]. No abnormalities, however, were detected in nerve conduction [129]. Whether vitamin E supplementation protects against oxidative lung damage in patients with CF is still speculative. A positive correlation between percent FEV_1 and plasma vitamin E levels in patients with CF was recently reported [130].

6.4. Vitamin K

As long as vitamin K was only supposed to be important in coagulation, a diagnosis of deficiency was exceptional and supplements were restricted to patients with haemoptysis, uncontrollable malabsorption from pancreatic disease, liver disease, intestinal resections or long-term use of antibiotics [131]. Recent studies indicate vitamin K acts as a cofactor in the carboxylation, not only of prothrombin involved in coagulation, but also of osteocalcin in bone formation [132]. Determination of proteins induced in vitamin K absence (PIVKA), a new sensitive method for the measurement of this vitamin, demonstrates that deficiency is common in CF especially in unsupplemented pancreatic insufficiency [133]. Based on the carboxylation state of these proteins in patients with CF, 5 mg vitamin K was supplemented weekly without reaching normal levels in these patients [134]. But in a recent study from Toronto unsuspected biochemical vitamin K deficiency was partly corrected by an oral supplement [135]. A water-soluble, oral vitamin K preparation is often given to patients with CF, even though adequate comparative data on the bioavailability of vitamin K from the standard preparation and the water-soluble micellar preparation are unavailable. The parenteral route should only be chosen to correct an acute symptomatic deficiency, in severe liver disease or malabsorption. Further studies are needed in patients with CF with liver disease, severe malabsorption, small bowel resections and long-term antibiotic use before the optimal dose of vitamin K is determined.

6.5. Water soluble vitamins

Water-soluble vitamins usually do not pose an appreciable problem in CF. Many patients with CF with exocrine pancreatic insufficiency have a disturbed Schilling test indicating an abnormal vitamin B12 absorption, but pancreatic enzyme preparations promote absorption of vitamin B12. Patients who underwent extensive resections of the terminal ileum need lifelong treatment with a parenteral administration of 100 μg vitamin B12 per month. In contrast, vitamin B12 deficiency in pancreatic sufficient patients with CF not taking pancreatic enzyme supplements is exceptional [136]. Plasma vitamin C concentrations are inversely related to age and different indices of inflammation [137]. The antioxidant role of vitamin C is currently under investigation.

7. Mineral and trace element deficiency

In the daily diet, macronutrients are needed for the body in relative large amounts and are important for the cell or the extracellular compartment. Micronutrients as cofactors are essential for enzymatic reactions or as structural elements of proteins.

7.1. Minerals

Sodium and chloride are the most important ions in the extracellular fluid [138]. The mean daily intake of sodium is between 6 and 9 g a day for adults, which is in excess of the daily minimal requirement (<3.5 g/day). Newborns need more sodium and chloride in relation to their bodyweight for the increase of extra

Table 2
Minimal daily requirements for sodium, chloride and potassium in normal individuals

Age	Sodium (mg)	Chloride (mg)	Potassium (mg)
<1 year	120–200	180–300	500–700
>1 year	225–500	350–750	1000–2000

Source: National Research Council, 1989. In CF more loss through sweat and stool can be anticipated, and has to be supplemented on an individual basis.

cellular volume. The minimal need is based on the concentration of breast milk (sodium 160 mg/l, chloride 385 mg/l, and potassium 500 mg/l). In the first 6 months the population reference intake (PRI) for sodium is 23 mg/kg per day, the recommended intake is 23–46 mg/kg per day. For newborn babies the acceptable intake for chloride is 35–71 mg/kg per day. The daily sodium loss in sweat is approximately 500 mg in adults. The loss may increase 10 times in CF during exercise in the sun, sometimes accompanied by hyponatraemia and alkalosis. In moderate climates the excess of sodium intake in food compensates this extra loss. The serum sodium concentration is regulated by the renin-angiotensin-aldosterone axis that diminishes the sodium excretion in the urine during activation. In most patients this balance is maintained. Since human milk is low in sodium, breast fed babies may need supplementation during fever or hot summer months.

Potassium is the most important intracellular cation, involved in nerve conductance, muscle contraction and blood pressure. Potassium loss with sweat is low. The mean potassium intake for adults is between 2 and 3.5 g daily. Rapidly growing young children need during increased growth velocity approximately 78 mg/100 kcal (recommended intake) or 35–78 mg/kg per day (acceptable intake) (Table 2).

Calcium is important for the mineralisation of the skeleton, muscle contractions and signal transmission in the nervous system [139]. Fat malabsorption and vitamin D deficiency are the main causes of low calcium uptake in the intestine [140]. Calcium intake in non-CF individuals is dependent on age and growth velocity. Children need 400 to 800 mg calcium and adolescents 800–1200 mg calcium daily. In CF, tetany, rickets or clotting abnormalities are rare. Plasma calcium levels and calcium excretion in the urine are normal. In young children with CF bone mineralisation is thought to be normal, but in adolescent and adult patients with CF bone mineral density and bone content is often diminished and spontaneous fractures are described [141]. Also phosphate homeostasis is strongly related to calcium and regulated by vitamin D [142]. Most food products are rich in phosphate and a deficient intake is exceptionally rare. Only young infants with low body weight are at risk for nutritional deficiency of phosphate. The ideal ratio of calcium to phosphate intake is 2:1.

Only 1% of the body store of magnesium (adult: 25 g) is in the extracellular fluid. Magnesium is important in the skeleton (60% of the magnesium pool) and muscles and in many biochemical processes. Normal serum levels are 0.7–1.0 mmol/l. Based on the concentration in human milk the recommended dose for infants and young children is 7 mg/kg per day and for adults 3.5 mg/kg per day. Hypomagnesaemia is characterised by tremor, tetany, neuromuscular irritability and seizures. Magnesium absorption is disturbed in pancreatic insufficiency and is closely associated with calcium and phosphorus. Urinary magnesium excretion is increased by aminoglycosides probably causing renal tubular damage [143]. Serum levels do not always correlate with the severity of symptoms.

7.2. Trace elements

The iron store in the body is 3–4 g of which 70% is in the red blood cells and 25% in ferritin and haemosiderin in liver, spleen and bone marrow. The transport protein in plasma is transferrin. Children need 5–10 mg of iron daily. Iron deficiency is frequent in CF and caused by multiple factors: inadequate dietary intake, malabsorption, chronic infection, and blood loss. Pancreatic enzymes may be responsible for impaired oral iron absorption and iron should not be supplemented in close proximity to pancreatic enzyme supplements [144]. It is unclear whether iron supplementation will improve the iron status, which is monitored by measuring serum ferritin levels in patients with CF. Ferritin levels can be increased during infection.

The total body zinc content is 2 g and most of it is intracellularly deposited in the skeleton, muscles, liver and skin. Red blood cells contain 0.9–1.5 mg zinc per 100 ml. Zinc has an important function in many enzymes. Deficiency is characterised by growth retardation, acrodermatitis, and disturbed immune function. Children need 5–10 mg/day and adults up to 15 mg. It is suspected that subclinical zinc deficiency due to fat malabsorption is wide spread in CF and is caused by zinc forming complexes with fat and phosphorus [145]. Pancreatic enzyme supplements improve zinc absorption [146].

Like zinc, copper is part of many enzymes and found mostly intracellularly in liver, muscle and bone. In the plasma copper is bound by caeruloplasmin. Copper deficiency results in anaemia, neutropenia, heart disorders, muscle weakness, immune disorders, pancreatic atrophy, and connective tissue impairment. Copper deficiency is only partially represented by plasma copper levels because caeruloplasmin is an acute phase protein. There is insufficient information to support supplemen-

tation of copper more than the age appropriate recommended daily allowance (RDA) [147].

Selenium is an essential part of the antioxidant glutathione peroxidase. Deficiency of selenium causes cardiomyopathy and muscle weakness. Glutathione peroxidase activity in red blood cells is a better indicator of selenium status than plasma values. In CF there is an indication that the selenium status is disturbed [148], however, at present, it cannot be recommended to supplement selenium in patients with CF. Pancreatic enzyme preparations contain 0.5–1.6 μg/g of selenium and this amount is sufficient to affect glutathione peroxidase activity [149].

Iodine is incorporated in hormones of the thyroid gland. Iodine deficiency does not occur in CF, since iodine is easily absorbed from food. Iodine requirements increase with age: 40 μg during the first 6 months to 150 μg at 10 years. Manganese is necessary for the antioxidant superoxide dismutase. The total body pool is 10–20 mg and supplementation for patients with CF is not needed. Similarly, molybdenum deficiency is extremely rare and does not need supplementation. Chromium plays a role in carbohydrate and lipid metabolism and protein synthesis and is important for growth. Patients with CF had normal plasma levels during supplementation of 0.5–0.75 μg/kg per day [150]. It is questionable if supplementation is necessary. Fluorine is found in tooth and bone and supplements are not required.

8. Antioxidant deficiency

In patients with CF, the antioxidant protective screen is markedly disturbed as a result of impaired status of glutathione, vitamin E and carotenoids such as β-carotene and lycopene. Occasionally low plasma concentrations of albumin, vitamin C and selenium are found. Glutathione deficiency has been described to occur both locally in the CF airways and systemically [151]. Glutathione is transported via the CFTR, suggesting that glutathione deficiency is intrinsically related to CF [152]. The glutathione status is also associated with nutritional status [153]. Carotenoids are highly lipophilic compounds not considered to be vitamins, of which the plasma and lipoprotein concentrations are very low in CF patients with exocrine pancreatic insufficiency. In addition to its provitamin A function, β-carotene acts as an antioxidant. Correction of poor vitamin E and β-carotene status to normal enhances the resistance against oxidation of plasma lipoproteins [125,154], decreases plasma lipid peroxidation [154–156] and reduces inflammation [157]. For counterbalancing the enhanced reactive oxygen species production due to chronic inflammation, full correction of the antioxidant screen is warranted. Future studies should address the question as to whether the final goal of antioxidant supplementation is to achieve plasma concentrations in CF higher than those in healthy subjects.

9. Prevention of malnutrition and treatment of pancreatic insufficiency

Prevention of malnutrition requires early intervention. Therefore early diagnosis is of importance and may be achieved by neonatal screening [9]. Following diagnosis, frequent reviews by a specialist CF dietician are mandatory; during the first 12 months after diagnosis at least once every month, thereafter at least every 3 months. The frequency of clinical reviews depends on the clinical state, control of the malabsorption and weight gain. Patients on a special diet (e.g. vegetarian) should be monitored more closely.

The majority of individuals with CF can tolerate a normal to high fat diet if treated with pancreatic enzymes in doses (Tables 3 and 4) matched to fat intake [158]. A 3-day faecal fat study and dietary assessment is the best measure of fat absorption. The diet is quite often low in fibre but for some who experience recurrent abdominal pain, an increase in fibre intake to 30 g per day with additional water may reduce abdominal symptoms [159] and may lead to an improved appetite and energy intake in some patients. In children with CF and well-controlled absorption and only mild chest infections, a normal energy intake may be sufficient. However, if the nutritional state and/or growth are abnormal, the diet should provide in excess of 20% of the recommended daily amount and high-energy dietary supplements or even enteral tube feeding may be required. As energy requirements vary so widely it is important that an assessment of each individual's needs is undertaken.

9.1. Infant feeding

Infants with CF fed on breast milk [5] achieve normal weight gain and growth by the age of 1 year as do infants on normal formulae [6] and those fed on a predigested medium chain triglyceride containing formula [160]. For the first year of life the ESPGHAN recommendation of exclusive breast feeding for the first 4–6 months of life is appropriate for the infant with CF. [5]. If breast-feeding is not possible or there is insufficient milk, cows' milk-based infant formulae can be used [6,160]. Whole cows' milk should not be given during the first year of life. Infants who receive a feed containing adequate energy and who are also given an appropriate dose of supplemental pancreatic enzymes should thrive satisfactorily irrespective of the type of milk [6,161]. Extensively hydrolysed protein formulae should be considered for infants who have undergone extensive gut resection for meconium ileus and for those with milk intolerance (e.g. cows' milk allergy or lactose intolerance) [162]. A feed containing medium chain

Table 3
Minimum enzyme content of pancreatic enzyme preparations

Name	Maker	Lipase	Protease	Amylase
Enteric-coated microspheres				
Cotazym	Thiemann			
10 000		10 000 Ph Eur u	375 Ph Eur u	6250 Ph Eur u
20 000		20 000 Ph Eur u	750 Ph Eur u	12 500 Ph Eur u
30 000		30 000 Ph Eur u	1125 Ph Eur u	18 750 Ph Eur u
40 000		40 000 Ph Eur u	1500 Ph Eur u	25 000 Ph Eur u
Nutrizym[a] GR	Merck	10 000 BP u	650 BP u	10 000 BP u
Pancrease	Janssen-Cilag	5000 BP u	330 BP u	2900 BP u
Enteric-coated minimicrospheres				
Creon	Solvay			
10 000		10 000 Ph Eur u	600 Ph Eur u	8000 Ph Eur u
25 000		25 000 Ph Eur u	1000 Ph Eur u	18 000 Ph Eur u
40 000		40 000 Ph Eur u	2000 Ph Eur u	30 000 Ph Eur u
For children		5000 Ph Eur u	200 Ph Eur u	3600 Ph Eur u
Enteric-coated minitablets				
Nutrizym[a]	Merck			
10		10 000 BP u	500 BP u	9000 BP u
22		22 000 BP u	1100 BP u	19 800 BP u
Panzytrat[a]	Knoll			
10 000		10 000 Ph Eur u	500 Ph Eur u	9000 Ph Eur u
25 000		25 000 Ph Eur u	1250 Ph Eur u	22 500 Ph Eur u
Pancrease HL[a]	Janssen-Cilag	25 000 BP u	1250 BP u	22 500 BP u

Note: For amylase and lipase 1 BP unit = 1 Ph Eur unit; for protease there is no direct equivalence between BP and Ph Eur units because of the use of different assay methods.
[a] Eudragit-coated.

triglycerides should be considered in patients with cholestasis or uncontrolled steatorrhoea. If weight gain is poor, additional energy supplements may be added to formulae or a high-energy infant formula used. A normal to high fat weaning diet is recommended depending on the infant's growth. The first 2 years are a period of very rapid growth; therefore close monitoring of the general condition, the nutritional state and the growth rate of the infant with CF is needed. If poor weight gain is related to an increase in frequency of chest infections, vigorous treatment of the latter will both improve the nutritional state and reduce the amount of pulmonary damage.

Treatment of acute and chronic lung infection normally results in an increase in bodyweight, which is related to a reduction in systemic inflammation [163–166].

9.2. Control of malabsorption achieved with current enzymes preparations

Enzyme preparations may differ in their enzyme content, which often varies with batches, in their dissolution characteristics in relation to the pH and to other constituents of the duodenal fluid [167] and in the size of the particles and their rate of exit from the stomach in relation to the meal. The practical details of administration, including adjusting the enzyme dose to the fat intake and the timing in relation to the meal will have a significant effect. Future studies are needed in this context.

Coefficients of fat absorption of between 85% and 95% of intake should be possible with presently available enzyme preparations [168–173]. Nevertheless, a substantial number of patients with CF do not achieve normal absorption [174]. Based on reports of fibrosing colonopathy, various guidelines for the use of pancreatic enzymes in CF have appeared [58,175–177]. Recommendations are summarised in Table 4.

9.3. Failure to control gastrointestinal symptoms

Sometimes, control of symptoms is not achieved even with a dose of enzyme equivalent to the recommended 10 000 IU lipase/kg per day [175] is given in an appropriate manner. The degree of residual malabsorption should be estimated and other gastrointestinal disorders should be considered. A progressive increase in enzyme dose without further investigations is not recommended [178]. Distal intestinal obstruction syndrome (DIOS) is characterised by recurrent attacks of abdominal pain with variable symptoms of obstruction and is relatively common in patients with CF [179]. An increase in pancreatic enzyme dose in patients with DIOS is likely to worsen the abdominal pain and constipation [22]. Other possible gastrointestinal problems include gastro-oesophageal reflux, which seems to be common both in infants [180,181] and older patients

Table 4
Recommendations for pancreatic enzyme supplementation therapy in CF

Infants	
•	Use a microsphere or minimicrosphere preparation
•	For every 120 ml infant formula or breast milk give as the initial dose of one-quarter to one-third of a capsule of standard strength pancreatin (as Creon 10 000 = 2500–3333 IU lipase; as Pancrease = 1666–2500 IU lipase). These doses equate to approximately 400–800 IU lipase per g of dietary fat.
•	Mix the enzyme microspheres or minimicrospheres with a small amount of infant formula or expressed breast milk or fruit puree and give from a spoon directly before the feed.
•	Increase the dose gradually according to clinical symptoms, appearance of the stools and objective assessment of weight gain, growth and absorption.
•	Once solid food is introduced, individually titrate enzyme dose according to the fat intake. Regular advice from a dietician is mandatory for best results.
•	Aim to keep the lipase intake below 10 000 IU per kg body weight per day.
Older children and adults	
•	Initial dose of 1–2 capsules of standard pancreatin preparation (as Creon 10 000 = 10 000-20 000 IU lipase; as Pancrease = 5000–10 000 IU lipase) per meal and a half to one capsule with fat containing snacks.
•	One paediatric unit has continued to use high strength microsphere capsules (Creon 25 000) without problems.
•	Enzymes should be given with all fat containing foods and supplements. The dose should be worked out individually, initially with the help of a dietician, and varied according to the fat intake. Dose requirements can vary widely between 500 and 4000 IU lipase per gram of dietary fat.
•	The capsules should be swallowed whole at as early an age as possible and many children will manage this by 3 or 4 years, some very much earlier. If removed from the capsules, the microspheres should *not* be sprinkled on or mixed with the whole meal but should be mixed with a little fluid or food and immediately given from a spoon in one swallow. They should not be crushed or chewed.
•	Enzymes are best given at the beginning or early in the meal, e.g. half the dose at the beginning and half in the middle of the meal.
•	The dose is gradually increased until the symptoms are controlled when evidence is sought that absorption has been controlled.
•	Patients and parents should be encouraged to discuss any problems they may have with adherence to enzyme treatment.
•	In tube or gastrostomy fed patients pancreatic enzymes should be given before and after the feed.

From*:* Littlewood JM, Wolfe SP. Control of malabsorption in cystic fibrosis. Paediatr Drugs 2000;2:205–222.

[182], inflammatory bowel disease [183], pancreatitis in pancreatic sufficient patients [184], short bowel with bacterial overgrowth and adhesions after intestinal surgery, liver and gall bladder disease [185], cows' milk protein allergy or lactose maldigestion [162] and even intolerance to the porcine enzyme preparations [186].

Patient adherence to treatment provides another problem in the control of gastrointestinal symptoms and the role of an experienced dietician to discuss the practical details of treatment in such circumstances cannot be over emphasised.

Reduction of gastric acid has improved absorption in patients with CF where control was poor even with enteric-coated acid resistant enzymes. Treatments have included cimetidine [187]; ranitidine [188] omeprazole [189] and lansoprazole [190] Long-term side effects of this group of drugs have not been investigated. Taurine-conjugated bile acids are in relatively short supply due to the gastrointestinal losses, which occur in CF. There is a relatively greater compensatory production of glycine-conjugated bile acids [52]. Therefore, in CF taurine-conjugated bile acids, which are more efficient at lipid solubilisation, are deficient in plasma and bile [53]. There is still controversy as to whether or not oral taurine corrects the deficiency and improves the malabsorption. Further studies are needed [191].

10. Side effects of pancreatic enzymes

Hyperuricaemia and hyperuricosuria, which occurred with the older less pure pancreatic extracts, are no longer a problem with the modern microsphere preparations [192]. Soreness of the mouth may occur with powdered preparations or if acid resistant microspheres are chewed or held in the mouth and dissolve with a pH of greater than 5.5. If older powdered preparations are used in breast-fed infants, soreness both of the infant's mouth and of the mother's nipples may occur.

Perianal irritation may result from the passage of significant enzyme activity in the stools if intestinal transit is rapid or the enzyme dose excessive. The porcine origin of the pancreatic enzymes causes apparently insignificant immunological response in most patients [193], however, this has been suggested a possible aetiological factor in fibrosing colonopathy (FC) [194]. Severe acute and chronic gastrointestinal allergic reactions [186] and general allergic reactions may occur in people administering powdered enzymes to infants with CF [195,196]. In patients who have had chronic significant fat malabsorption a too rapid increase in enzyme dose may cause severe constipation.

Fibrosing colonopathy (FC) was first reported in 1994 [197,198]. The exact pathophysiology is still uncertain, however, the progressive increase in pancreatin dose prescribed for persisting intestinal symptoms appears to have been a major factor in reaching the very high doses implicated in FC [198,199]. Toxicity from the co-polymer Eudragit L30 D55, an acrylic resin based on polymethacrylic acid and polyacrylic acid esters, used as an enteric coating by some pancreatin preparations, has also been proposed [198,200,201]. However, acrylic resin is widely used in many different preparations and toxicity the role in the causation of FC is not generally accepted [202–204]. A list of co-polymer coated preparations is given in Table 3, together with phthalate-coated alternatives.

With the increased awareness of FC, pancreatin dosing has become more conservative with the recommendation not exceeding 10 000 USP lipase/kg per day; this and restriction of high strength preparations ($>$25 000 IU lipase/capsule) to adult populations has resulted in a dramatic fall in the incidence of FC in Europe.

11. EFA treatment

Dietary treatment of patients with CF should aim at avoiding clearly subnormal levels of EFA and LC-PUFA. Strategies to achieve that goal include an adequate supply of energy, polyunsaturated fatty acids of both the n-6 and the n-3 series in balanced proportions, as well as antioxidants. Several studies have failed to demonstrate any general improvement by supplementation of EFA [205,206] but physiological improvement in liver steatosis, kidney function and sodium transport have been reported [207,208]. However, excessive intakes of EFA and LC-PUFA carry the risk of adverse effects, such as enhanced lipid peroxidation and unbalanced synthesis of specific eicosanoids, with clinical consequences.

Beneficial effects of supplying increased intakes of specific fatty acids, or groups of fatty acids, have been proposed. High supplies of fish oil rich in the omega-3 fatty acid EPA reduce the liberation of proinflammatory leukotrienes from granulocytes of patients with CF in vitro [209] and in vivo [210] and were reported to improve pulmonary function in some preliminary studies [211,212], this observation deserves further evaluation. Very high intakes of the omega-3 fatty acid DHA have been reported to reduce organ damage in a mouse model of CF. Whether or not comparable clinical benefits can be achieved in patients with CF supplemented with high doses of DHA should be evaluated. Based on the available evidence it is recommended that patients with CF should receive an adequate dietary intake of omega-3 fatty acids as is recommended for the general population, it is considered premature to recommend high pharmacological doses of specific omega-3 fatty acids prior to further characterisation of the efficacy of such intervention. In a controlled trial, URSO therapy for 6 months led to an improvement in EFA status [109].

12. Vitamin supplementation

Clinical evidence of vitamin deficiency is rare and there is no uniformity on the goals of supplementation. Relevant questions are how to prevent isolated biochemical deficiencies and subclinical abnormalities. The present consensus favours prophylactic substitution of those vitamins for which low blood levels or deficiencies have ever been described. The initial dose proposed usually is adequate to normalise blood concentrations in most patients with CF without causing hypervitaminosis. It is prudent to measure vitamin blood levels after a few months and after any change in the treatment of the malabsorption because this can influence vitamin absorption. Subsequent supplementation should be adjusted according to the patient's blood levels; afterwards annual monitoring is sufficient [117].

12.1. Vitamin A

The vitamin A intake should be high enough to achieve serum concentrations in the normal range without provoking side effects. This can be achieved with daily doses between 4000 and 10 000 IU of a fat-soluble preparation [114]. Water-soluble or water-miscible forms of vitamin A preparations have not been studied in CF. As absorption and metabolism of vitamin A differ between individuals, serum concentrations should be estimated at least once a year and 3–6 months after any change in dose. If plasma levels are low despite supplementation to the above levels consideration should be given to patient compliance and the RBP and the zinc level should be checked. In view of the potential toxicity of vitamin A, supplementation should never exceed 20 000 IU if the RBP is low. Special consideration must be given to vitamin A supplementation during pregnancy. A relationship has been suggested between the incidence of birth defects and high vitamin A intake

(>10 000 IU/day). In CF serum levels should be checked at the start of pregnancy. If plasma levels are high it is recommended the dose is reduced. If levels are low or normal supplementation should continue at a level less than 10 000 IU/day.

12.2. B-Carotene

In patients with CF with pancreatic insufficiency a daily dose of 0.5–1 mg/kg β-carotene corrected very low plasma and lipoprotein concentrations to normal [156–158]. However, plasma concentrations need to be monitored to make sure that above normal concentrations will not be achieved in the individual patient, given the fact that in smokers, a group of subjects also exhibiting oxidative stress, higher than normal plasma β-carotene concentrations were associated with serious side effects.

12.3. Vitamin D

As sunlight is the major source of vitamin D for the body, serum concentrations will depend largely on endogenous production in the skin and this will differ between individuals [213].

Decreased serum concentrations of 25-OH-CC have been described in patients with CF receiving daily oral supplementation of up to 2000 IU of vitamin D [214]. No cases of hypervitaminosis D were reported with this concentration in patients with CF. No studies are available on the effect of intermittent large doses. To keep blood levels within a normal range, a daily dose of between 400 and 2000 IU is required. Recent evidence suggests that the serum level should be maintained within the upper part of the normal range to ensure optimal bone health [214]. In severe hepatocellular disease 25-hydroxylation is impaired and therefore 25-OH-vitamin D is preferred for supplementation [214].

12.4. Vitamin E

Clinical deficiency states are exceptional in patients with CF [130], but enhanced susceptibility to lipid peroxidation has been demonstrated to occur in patients with low vitamin E status [126]. Therefore regular vitamin E supplementation is recommended. As vitamin E is non-toxic there is no objection to using up to 400 IU daily (=400 mg all-rac-α-tocopheryl acetate=450 mg dl-α-tocopheryl acetate or 268 mg RRR-α-tocopherol) [124]. In animals and humans side effects were only seen when excessively high amounts were given. The more expensive water-soluble form has no advantage over the fat-soluble form, provided the latter is taken with pancreatic enzymes [124,215]. RRR-α-tocopherol and all-rac-α-tocopheryl acetate were shown to be equally effective, when given at a dose of 400 mg IU/day [124]. With that dose a normal resistance to oxidation of lipoprotein could be achieved [126]. It has been recommended to use for the interpretation of adequate levels of the plasma, tocopherol/total lipid or cholesterol ratio as an index of vitamin E status particularly when levels are low, because the vitamin E levels rise with lipids.

12.5. Vitamin K

Routine supplementation with vitamin K has always been controversial. But recent studies have revealed unsuspected biochemical deficiency, which may be an important factor in the osteoporosis in CF [134]. Patients with demonstrated or suspected deficiency should be given 10 mg daily. However, the dose required to correct PIVKA levels is still controversial. A recent randomised prospective study found better biochemical parameters with a supplementation of 5 mg weekly [134]. Even then normal levels were not achieved in all patients [135]. Probably better results are achieved with a daily supplement [136]. For systemic substitution, an oral water-soluble form should be given; parenteral administration should be reserved for correction of acute symptomatic deficiency, in severe hepatocellular disease or uncorrectable malabsorption.

12.6. Water-soluble vitamins

Patients who underwent extensive resections of the terminal ileum need lifelong treatment with parenteral administration of 100 μg vitamin B_{12} per month. A supplement of at least 100 mg vitamin C per day should be prescribed for patients with an unbalanced diet, deficient in vitamin C. No other water-soluble vitamin supplements are needed.

12.7. Conclusion

The doses proposed in Table 5 are those reported to achieve normal plasma concentrations in patients with CF without liver disease that will not cause toxicity. The availability of a preparation that combines the vitamins at the required doses could help improve compliance and make life of patients with CF more convenient. Fat-soluble vitamins need to be taken at the same time as a meal for which pancreatic enzymes are required.

13. Mineral and trace element supplementation

13.1. Minerals

Sodium and chloride supplementation is usually not necessary except during exercise in hot climates when extra salt is recommended (for minimal need see Table

Table 5
Recommendations for vitamin supplements in CF

Fat soluble vitamins	CF patients needing supplements	Starting dose
A	EPI	4000–10 000 IU[a]/day
D	EPI, northern countries	400–800 IU[b]/day depending on serum level
E	All	100–400 IU[c]/day
K	EPI, cholestasis	1 mg/day to 10 mg/week
B12	Schilling test <45% after ileal resection	100 μ i.m./month
Other water soluble vitamins	None if dietary intake is normal	

EPI, exocrine pancreatic insufficiency. Conversion factors: IU to mg: [a]vitamin A: IU×0.3=μ; [b]vitamin D: IU/40=μ; [c]vitamin E: all-rac-α-tocopheryl acetate: IU=mg; RRR-α-tocopherol: IU/1.49=mg.
The need for vitamin supplementation in pancreatic sufficient patients should be assessed on an individual basis according to plasma levels.

2). Moreover, breast fed infants are not always able to meet their sodium chloride needs and may require supplementation, particularly when exposed to high ambient temperatures or at high water losses due to fever, sweating or tachypnoea. Children and adults with CF need oral calcium supplementation if their diet is found to be deficient.

During long-term treatment with aminoglycosides and severe malabsorption patients with CF may need extra substitution of magnesium.

13.2. Trace elements

The need for iron supplementation should be determined by the plasma transferrin saturation and not given simultaneously with pancreatic enzymes. In growth retardation and severe steatorrhoea zinc should be supplemented. Selenium supplements may be needed in special areas (e.g. in Switzerland, Austria). However, these should be used with caution, as there is a narrow range between supplementary and toxic doses.

14. Supplementation with antioxidants

Vitamin E is the most important fat-soluble antioxidant and the doses recommended for supplementation are presented above. However, higher doses will be required if the intake of polyunsaturated fatty acids (such as DHA) is increased above the average dietary intake. Supplementation with vitamin C and selenium, which represents an integral constituent of the antioxidant enzyme glutathione peroxidase, and glutathione precursors or derivatives need to prove to be beneficial but randomised controlled studies are required before their use can be recommended.

15. Refeeding the malnourished child

In many CF studies a relationship has been shown between body weight and lung function [216], but it is unclear what is cause and what is effect [217]. Reasons for a decrease in energy intake include anorexia, feeding disorders (neonatal tube feeding), depression, interactions with parents, oesophagitis, DIOS, iatrogenic fat restriction, decreased appetite by concomitant drugs or pulmonary inflammation and lack of general well being. In most cases early intervention is extremely important to prevent negative long-term effects. Intervention is often complicated because the multifactorial nature of the problem.

Interventions include behavioural treatment, psychological support, dietetic advice, oral supplementation, nasogastric tube feeding, gastrostomy feeding and parenteral feeding. Although there are reports that eating is a problem for patients with CF [218], a positive effect of any form of nutritional intervention with oral supplements is still unproven [219,220] possibly due to small and uncontrolled studies which differ in design, parameters and outcome measures. It is important to start interventions early [217] (Table 1).

15.1. Recommendations

15.1.1. Oral feeding

0–1 year: Breast feeding is the preferred way of feeding infants and also should be recommended for those with CF. Mothers of breast-fed infants may need to be encouraged to feed more frequently to increase milk formation and thus meet their infant's energy needs. Some breast fed infants may benefit from sodium chloride supplementation, particularly at high ambient temperatures or with increased water losses due to fever, diarrhoea, tachypnoea or increased sweating.

Formula fed infants will usually receive regular formula that can be supplemented with up to a total carbohydrate content of 10–12 g/100 ml and a total fat content of 5 g/100 ml which will achieve an energy density of approximately 1 kcal/ml. Supplementation should be gradually increased up to these levels. A special dietetic product for infants with a high energy

content could also be used but may be less flexible and more expensive. The volume of feed should be adapted to achieve normal weight gain and growth velocity, which often means that higher volumes will need to be fed than in healthy babies. Solids should be introduced at the normal age of 4–6 months. Most infants with CF will thrive satisfactorily on a normal weaning diet. If the infant is failing to thrive, higher fat foods may be used, with appropriate adjustment of the pancreatic enzymes.

2–5 years: A normal to high fat diet should be advised depending on growth and nutritional status. In the past oral supplements were often unpalatable, however, recent studies show that some supplements are well accepted by this age group. A compromise must be found between palatability, volume and the optimal composition to obtain maximal compliance. For children in this age range specific commercially products are available now.

5 years: Standard adult supplements can be used and the choice is often directed by the taste of the patient and long-term acceptance. Preferably, high energy density formulae should be used.

15.1.2. Supplements

There are many types of nutritional supplements available. Palatability, volume and the optimal composition determine the choice. For children of approximately 1–5 years age specific commercially available products can be used. Standard adult supplements are suitable for children over 5 years. The choice of the supplement is often determined by the taste preference of the patient to obtain maximal compliance. High-energy dense preparations should be used wherever possible.

Supplements should be given before or after meals or before bedtime to ensure that the appetite for normal food is maintained. At the present time there is a lack of evidence to support the use of dietary supplements [219]. A large multicentre trial is currently addressing this issue in the UK.

15.1.3. Tube feeding

Tube feeding can be administered by naso-gastric tube or by gastrostomy, patient's preference determining the choice of the route. Preferably, tube feeding should be given overnight with the aim to maintain normal dietary intake during the day. Gastro-oesophageal reflux (GER) may be a problem in some patients and should be monitored closely before feeding is recommended. If GER is documented, a Nissen's fundoplication may be indicated prior to gastrostomy insertion. In patients with borderline glucose intolerance nocturnal hyperglycaemia should be monitored and if necessary treated with insulin. Normally, a high calorie non-elemental formula can be used. If this is not tolerated, and in rare instances, individual patients may benefit from elemental or medium chain triglyceride (MCT) containing formulae. Because of the slow flow of fat infusion absorption is generally adequately controlled by taking a small dose of enzymes at the start and during the feed. If patients awake spontaneously they can also take extra enzymes during night.

15.1.4. Total parenteral nutrition

Total parenteral nutrition is not recommended for long-term treatment, but may be useful for short term support in infants and children after major (GI) surgery and in the severely ill patient waiting for a lung or liver transplant. Several studies have shown an improvement in nutritional status with supplementary parenteral feeding [221,222].

16. Treatment of the malnourished adult

The goal of treating the malnourished adult is to increase lean body mass [21]. Initially a high fat and high calorie diet may be used, but oral supplements are often needed. Oral supplements should be highly palatable and provide a large amount of calories in a small volume, preferably by having a high content of fat. The main disadvantage of oral supplements is their influence on normal appetite, thereby adversely affecting the energy intake. However, the use of palatable high calorie oral supplements showed an overall increase in daily energy intake. If dietary interventions, including oral supplementation, fail to increase bodyweight, one should consider nasogastric tube or gastrostomy feeding (PEG). Percutaneous sonographic gastrostomy (PSG) can be performed under local anaesthesia by an experienced radiologist guided by ultrasound [223] or by a gastroenterologist using fluoroscopic guidance. Enteral feeding offers the possibility of feeding overnight, thereby not influencing the patients' appetite during the day [224,225]. The formula used for tube feeding may be non-elemental provided that enzymes are taken at the start and preferably during the nocturnal feeding [226] (see Section 15.1). Parenteral nutrition is generally not recommended since it is limited by volume, immobilises the patient and increases the risk of sepsis [227]. For these reasons the use of parenteral nutrition is usually restricted to when the GI tract is non-functional or in severely malnourished patients awaiting transplantation.

When hyperalimentation is given as the sole intervention in malnourished adult patients with CF, body weight will increase but lean body mass may remain unchanged [228]. Since increase of muscle mass is an important target, the combination of nutritional support with specific muscle stimulation appears a relevant option. Combining nutritional support with an exercise programme may result in an increase in lean body mass, maximal

ventilatory capacity, oxygen uptake and maximal exercise capacity [229–231].

17. The important questions and answers

Q1. Does a nutritional deficit exist in CF patients and, if so, what impact does it have on disease progression and survival?

A1. Many patients with CF present with below normal weight and/or height. Even with treatment, malnutrition may occur leading to reduced weight gain and growth and nutritional deficiencies, which are associated with a more rapid progression, the disease and shortened survival. Nutritional deficits may be responsible for the delay in the onset of puberty and menarche in teenagers with CF. The nutritional state of patients has steadily improved over the years and is likely to be one of the major factors contributing to the increased survival in recent years. Provided the chest infection and associated inflammation are treated effectively, prevention and early treatment of nutritional deficits are associated with improved growth and respiratory function and are likely to improve prognosis.

Q2. How does malnutrition present in CF and how do we measure it?

A2. Malnutrition may present as underweight, subnormal longitudinal growth, or deficiencies in one or more single nutrients. Underweight is defined as a weight for height of less than 90% using appropriate normal values for the population or in adults, body mass index of less than 18.5 kg/m^2. In children, BMI values should be interpreted on the basis of gender-specific centile charts or *Z* scores. Standard deviation scores give similar information and are more convenient for statistical calculations. In the absence of normal values the longitudinal assessment of nutrition and growth is particularly important. Knowledge of the puberty state is necessary for the adequate assessment of growth over the age of 10 years. Assessment of diet, clinical and laboratory indicators of nutritional status should be performed at least annually. A longitudinal assessment is important.

Q3. What are the causes of malnutrition in CF?

A3. Malnutrition in CF has several causes including intestinal malabsorption, inadequate intake and increased energy requirements. Maldigestion and malabsorption, particularly of fat and protein, are early and severe in most patients. The most important cause is pancreatic insufficiency with inadequate secretion of enzymes and bicarbonate; other factors include impaired mucosal uptake, altered motility, liver disease and bile salt abnormalities and structural abnormalities due to previous bowel surgery. Energy intake may be inadequate due to poor appetite secondary to chronic pulmonary and gastrointestinal disease, acute infection or psychosocial problems causing abnormal eating behaviour. Energy requirements are increased due to chronic infection and inflammation, the excessive work of breathing and possibly secondary to the primary genetic defect.

Q4. Are essential fatty acids reduced in plasma and tissues of CF patients, and which mechanisms are responsible?

A4. Many CF patients have low plasma and tissue contents of linoleic acid and of omega-3 long-chain polyunsaturated fatty acids, such as eicosapentaenoic acid and docosahexaenoic acid. Omega-6 long-chain polyunsaturated fatty acids such as arachidonic acid are more variable. These changes have been related to a variety of physiological impairments and adverse effects and are considered as essential fatty acid deficiency. Possible mechanisms that lead to polyunsaturated fatty acid depletion include fat malabsorption, underweight and negative energy balance with an increased beta-oxidation of polyunsaturated fatty acids, and enhanced peroxidative destruction of polyunsaturated fatty acids due to poor antioxidant status and high oxidative stress. Moreover, the conversion of essential fatty acids to long-chain polyunsaturated fatty acids may be altered, and linoleic acid turnover and arachidonic acid release from phospholipids may be increased.

Q5. Is there evidence for vitamin deficiency?

A5. Blood levels of fat-soluble vitamins are frequently low in patients with CF. Biochemical evidence of vitamin A, vitamin D, vitamin E and vitamin K deficiency is frequently found even in the absence of clinical symptoms. Deficiencies of water-soluble vitamins are rare.

Q6. Is there evidence for mineral and trace element deficiency?

A6. Patients with CF are at risk of salt depletion and metabolic alkalosis in particular during fever, hot weather and exercise. They may suffer from mineral and trace element deficiency, including chloride, sodium, calcium, magnesium, zinc, iron and selenium.

Q7. What is the strategy to prevent malnutrition?

A7. Early diagnosis of CF by neonatal screening and early recognition of CF specific complications and non-CF related disorders, followed by appropriate treatments in specialised CF centres including optimal treatment of pulmonary infection, is recommended. There should be frequent and regular surveillance of the patients including expert dietary advice. For dietary intake in the first year of life the ESPGAN recommendations should be followed including exclusive breast-feeding in the first 4–6 months of life but if necessary a normal infant formula can be used. If the child fails to thrive, early intervention is mandatory. If children are gaining weight normally on a normal diet this can be continued. No fat limitations and no advice to increase fibre intake should be given. At all ages there should be close attention to behavioural factors, which may compromise adherence to medical treatment and food intake. Patients on special

diets (e.g. vegetarians) should be monitored particularly closely.

Q8. Does aggressive treatment of pulmonary disease in CF influence nutritional state?

A8. Malnutrition, infection, inflammation and disturbed immune function create a vicious cycle in which each factor in turn may exacerbate the other. Effective treatment of lung infection has been demonstrated to improve the nutritional status.

Q9. Does treatment of the nutritional status influence lung disease?

A9. Nutritional interventions have been shown to inhibit the decrease in lung function, thereby improving survival in patients with CF.

Q10. How do we treat pancreatic insufficiency?

A10. All patients with CF who have evidence of malabsorption due to pancreatic insufficiency should be treated with pancreatic enzymes using standard preparations. Special attention has to be paid to other conditions if fat malabsorption, poor growth or underweight persist in spite of adequate dosing. Recommendations are summarised in Tables 3 and 4.

Q11. What is the significance of fibrosing colonopathy (FC)?

A11. Although the exact pathophysiology of FC is still unknown, the progressive increase in enzyme dose in response to persisting symptoms was a major factor in reaching the very high doses implicated in the cause of fibrosing colonopathy. Enzyme doses in excess of 10 000 IU lipase/kg per day should only be used with caution and after excluding other causes of malabsorption and persisting gastrointestinal symptoms.

Q12. Is there an influence of ursodeoxycholic acid (URSO) on nutritional status in CF patients with CF related liver disease?

A12. URSO may enhance biliary bicarbonate secretion and bile flow. Some studies have provided indications for positive effects of URSO on biochemical parameters indicating liver disease, the bioavailability of dietary lipids and lipid soluble vitamins, and on weight gain which deserve further evaluation.

Q13. Is there a role for treatment strategies targeting essential fatty acid status in CF patients?

A13. Dietary treatment of CF patients should aim at avoiding subnormal levels of essential fatty acids and long-chain polyunsaturated fatty acids. Energy, antioxidants and polyunsaturated fatty acids of both the omega-6 and the omega-3 series should be adequately supplied in balanced proportions. Fish oil preparations have an anti-inflammatory effect. Their effect on pulmonary function deserves further evaluation. Similarly, beneficial effects of high amounts of DHA in CF mice need to be substantiated in CF patients. CF patients should consume omega-3 fatty acids in amounts as recommended for the general population.

Q14. What vitamins need to be supplemented, in which doses and how?

A14. In general fat-soluble vitamins should be given to patients with CF. Recommended doses are given in Table 5. Vitamins should be given with a fat containing meal and pancreatic enzymes. The dose of the vitamins should be sufficient to achieve and maintain normal blood concentrations. While there is little risk of overdosing with vitamins E and K, caution is necessary for vitamins A and D.

Q15. What minerals and trace elements need to be substituted?

A15. During exercise, in hot environments and during fever, sodium and chloride supplementation is recommended. During long-term treatment with aminoglycosides patients with CF may need additional magnesium. Iron and zinc deficiency should be corrected and results controlled biochemically.

Q16. How should we re-feed the malnourished child?

A16. In case of malnutrition or weight loss there should be a full re-evaluation of all the possible causes that may affect the nutritional state. If nutritional intervention is indicated, guidelines can be used. The first approach should be to ensure maximal energy intake using normal or energy-dense foods. Recommendations are given in the table. Supplements should be given between or after meals or before bedtime to ensure that the appetite for normal food is maintained. Tube feeding can be administered by naso-gastric tube or by gastrostomy, patients' preference determining the choice of the route. Preferably, tube feeding should be given overnight with the aim to maintain normal dietary intake. Total parenteral nutrition is only recommended for special indications.

Q17. How do we re-feed the malnourished adult?

A17. The indication for supplemental feeding either by oral supplements or tube feeding is the same in adults as in older children and adolescents. Monitoring for impaired glucose tolerance is needed. Psychosocial issues including body image should be addressed. An exercise-training program with the aim to increase lean body weight should accompany re-feeding in adolescents and adults.

Q18. Should anabolic steroids be used in re-feeding the malnourished CF patient?

A18. In a very limited number of CF patients it has been shown that megestrol acetate, a progestagon, may temporarily lead to an increased appetite, an increase in body weight with an increase in lean body mass and pulmonary function. Disadvantages are the possible development of diabetes, inhibition of growth, adrenal suppression, cardiomyopathy and behavioural problems including depression. Because of the side effects and the limited data available, anabolic medication should not be used in routine clinical practice.

Q19. Which future studies should be carried out to find more evidence for optimal nutrition in CF?

1. Long-term studies concerning the effect of antioxidants, particularly studies involving vitamin E, C, β-carotene and selenium, on clinical progress, respiratory function and nutritional status.
2. Long-term supplementation studies measuring vitamin K status and bone mineral density. The relationship between antibiotic therapy, gut flora and vitamin K status should be studied. In general drug-nutrient interactions should be determined and studied.
3. Quality vs. quantity in nutritional support.
4. Eating disorders and behaviour—categorisation, prevention, treatment and intervention studies.
5. Factors affecting adherence to enzyme therapy.
6. Reasons for failure to correct levels of nutrients.
7. Optimal levels of various nutrients for people with CF.
8. Evaluation of appetite stimulants.
9. Value of new prokinetic drugs.
10. Benefit of specific anti-inflammatory treatment, e.g. anti-TNF.
11. Role of leptins in cystic fibrosis.
12. Value of high-energy oral supplements.
13. Ideal feeds for enteral feeding.
14. Best enzyme regimen for overnight feeds.
15. Possibility of delaying pancreatic insufficiency.
16. Role of acid suppression in improving steatorrhoea.
17. Optimal prevention and management of osteoporosis.
18. Confirmation and study of reduced head circumference brain development and fatty acid status during infancy.
19. Early intervention in the development of diabetes mellitus. At what stage do we intervene?
20. Use of anabolic steroids.
21. Treatment with DHA or fish oil.
22. Role of probiotics in nutrition and infection.
23. Effect on nutritional status of continuous antimicrobial treatment, started soon after diagnosis following neonatal screening.
24. Optimisation of oral supplements.
25. Further knowledge of the homeostasis of calcium, the lipid peroxidation and role of selenium and zinc deficiency in young children.
26. The potential effects of URSO on nutritional status, in subgroups of patients with CF who have different disease states and conditions.
27. The effects of supplying increased intakes of specific fatty acids, and of groups of fatty acids such as long-chain omega-3 fatty acids, should be evaluated.
28. Relationship of fatty acids and immune functions and neurological development.

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