Authors: Elisabeth Stamm, Estelle Yersin, Laurent Chabal, Pauline Coti Bertrand, Corinne Challet, Laetitia-Marie Petit, Angela Koutsokera, Alain Sauty

1. GENERAL CONSIDERATIONS

- Malnutrition is the consequence of an imbalance between energy intake and energy needs. CF patients are at risk for undernutrition because of disproportionately high energy needs compared to the energy intake.
- Undernutrition influences CF patient outcomes adversely:
  - The relationship between nutrition and respiratory function is well established as FEV_1 decreases with lower body mass index (BMI) **(Figure 1)**.
  - Undernutrition and deficiency of nutrients, such as essential fatty acids or fat-soluble vitamins, have also a deleterious effect on muscle function, immune defenses and may also be related to CF-related liver disease and osteoporosis **(Figure 2)**.
  - Undernutrition is an independent risk factor for morbidity and mortality.
    Of note, emphasis on optimal nutrition at all ages and the introduction of high-calorie, high-fat diet as the standard of CF care are considered turning points in the history of CF leading to improved survival.
- **Table 1** summarizes predisposing factors for undernutrition in adult CF patients.
- The prevalence of undernutrition in adult CF patients varies from 8-38% depending on the used definition, the country, the patient's age and the severity of CF.
  - In Switzerland, according to the 2016 ECFS Registry report, the median BMI is 21.5 kg m^2 for adult male patients and 20.3 kg/m^2 for adult female patients, values which are slightly lower than the **BMI recommended by the ESPEN-ESPGHAN-ECFS guidelines which is 23 kg/m^2 for male patients and 22 kg/m^2 for female patients.**

Figure 1: Percentage predicted FEV_1 and BMI in adult CF patients 20 to 40 years old (reprinted with permission from the Cystic Fibrosis Foundation, 2017 Patient Registry Annual Data Report[1])

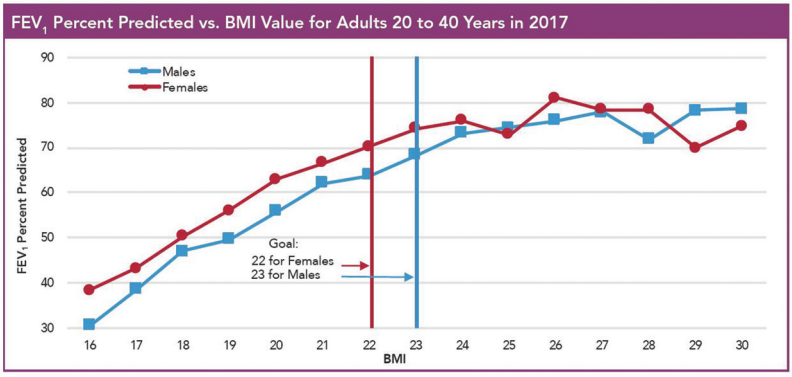
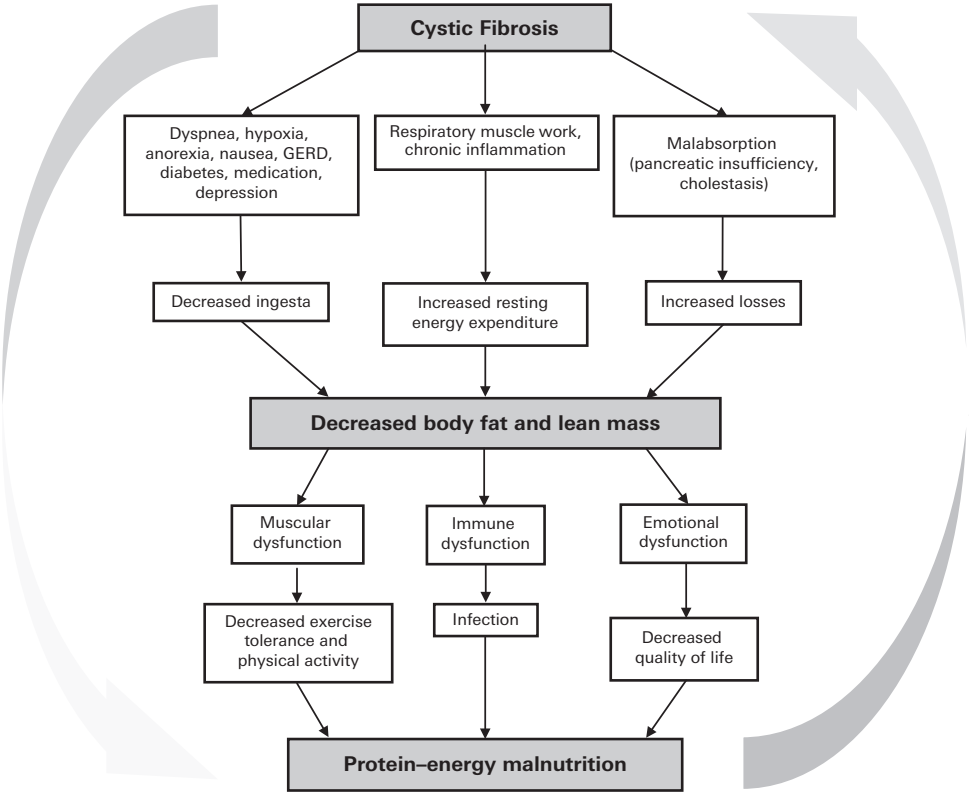


Figure 2: Consequences of malnutrition in CF (adapted from[2])



- During the transition period from pediatric to adult care, the pediatric CF team should inform the adult CF team about the evolution of the weight-for-height growth and also the measures taken to optimize growth and nutritional status during childhood.

2. NUTRITIONAL ASSESSMENT

- Nutritional assessment should be performed in close collaboration with dieticians.
- The main components of nutritional assessment **include the clinical history, the current body weight and weight changes, the physical examination, body composition and laboratory data (Table 2).**
- The ESPEN guidelines recommend:
  - Measurement of height and weight in adolescents, and weight in adults at least every 3 months to assess BMI.

- Routine measurement of
  - body composition **(see paragraph 2.1)** by different methods such as dual-energy X-ray absorptiometry (DEXA) or bioelectrical impedance (BIA) and
  - assessment of bone mineral density by DEXA (**see Chapter** "*Bone disease*").

- Patients at risk for malnutrition **(Figure 3 at the end of this chapter)** should be evaluated more frequently and their evaluation should be multidisciplinary (dietician, gastroenterologist, endocrinologist and psychologist).

Table 1: Risk factors for undernutrition in adult CF patients (adapted from[3])

Organs	Causes
Respiratory tract	Pulmonary exacerbations Severe lung disease Chronic rhinosinusitis
Digestive system	Pancreatic insufficiency Gastroesophageal reflux disease Recurrent pancreatitis Small bowel bacterial overgrowth Celiac disease Constipation Distal intestinal obstruction syndrome (DIOS) Diarrhea Inflammatory bowel diseases CF liver disease Motility disorders Eosinophilic gastrointestinal disease
Endocrine system	CF-related glucose intolerance/diabetes
Psychosocial	Body image disorders Anxiety/depression Stress Low income Time spent for treatment
Miscellaneous	Adverse drug effects

2.1 Body composition

- In practice, the study of body composition is based on 2 compartments:
  a) the fat mass (FM) and
  b) the lean mass (LM) which includes water, protein mass and bone mass.
- **Body composition is of major interest in CF since it gives information on the proportion of FM and LM and on the level of hydration of the patient.** At the beginning of a malnutrition state, it is common to observe a reduction of the FM with a preserved LM.
- Body composition can be assessed by a number of different techniques, however not all have been validated in CF.

Table 2: Components of the nutritional assessment (adapted from[4,5])

	Parameters	Frequency
Clinical history	– History of intestinal resection – History of recurrent pancreatitis – CF-related diabetes – CF liver disease – Nephrolithiasis – Bone disease	At first visit and when needed
Current history	– Gastrointestinal transit – Pancreatic sufficiency status – Food intake – Psycho-social problems that may influence nutrition	At each clinic visit (at least every 3 months)
Treatment	– Compliance – Pancreatic enzyme replacement therapy (PERT) – Vitamin substitution and calcium substitution, oral nutritional supplements and/or enteral nutrition, insulin etc	At each clinic visit (at least every 3 months)
Clinical assessment	– Emotional status, asthenia, strength, dyspnea – Appetite, satiety, gastrointestinal symptoms – Physical activity – Weight, height, BMI, weight loss or gain, muscle wasting	At each clinic visit (at least every 3 months)
Dietary review	– Food intake (24h recall, 3-5-day diet record*)	At least every 6 months
Body composition	– Triceps skinfold thickness and mid-arm muscle circumference – BIA – DXA (if available and clinically indicated)	At least annually
Standard biological assessment	– CBC, PT, electrolytes, renal and liver function, glucose level, C-reactive protein, albumin, prealbumin – Lipid status for patients >40 years old or CF-related diabetes or with a family history of hyperlipidemia	At least annually
Specific biological assessment	– Liposoluble vitamins: A, D, E and INR as an indicator of vitamin K status – Minerals : calcium, magnesium, phosphate	At least annually

BIA: bioelectrical impedance, BMI: body mass index, DXA: dual-energy X-ray absorptiometry
*For CF patients at risk for malnutrition, the 3-5-day diet record may be necessary to assess energy and nutrient intake more accurately.

- Anthropometry (tricipital skinfold and arm circumference): hand grip strength, tricipital skinfold thickness measurement using Holtain caliper and the arm muscle circumference are easy to perform. They can easily provide proof of subcutaneous fat loss or muscle wasting. Measures are compared to Frisancho's standard deviation percentiles.
- Bioelectrical impedance (BIA): BIA is a simple and noninvasive method that does not expose to radiation. It has been validated for a BMI between 18 and 34 kg/m^2 and it is also validated in the CF population. It is based on the difference between the electrical resistance of fat (high resistance) and lean (low resistance) components of the body.
  - Skin electrodes are placed on the patient and the resistance of electric power that flows through the tissues is converted into total body volume of water, fat mass and lean mass using standardized equations.
  - The test takes about 15 min to perform and requires minimal operator training.
  - It allows to evaluate changes of body composition over time. However, rapid hydroelectric variations disturb the measurement.
- DXA: initially used for bone density assessment, it has recently become the reference tool for body composition measurement.
  - It is considered to be accurate and precise. It not only makes possible to determine the total FM, but also the segmental FM.
  - Body composition DXA does not depend on weight or size, it exposes to low radiation and does not require special preparation.
  - However, it is not transportable, not applicable for extreme weight and height (height in the machine> 1.82 cm,> 135 kg), it is expensive and requires a radiology technician.

3. NUTRITIONAL INTERVENTION

3.1 Hydration

- Body composition assessment shows that, frequently, CF patients are not well hydrated. Signs of dehydration include thicker sputum and constipation.
- The recommended daily fluid intake is ≥ 35-45 ml/kg (2.5-3.0 L/day for an individual of 70 kg) (**Table 3**).
- Hydratation must be adapted in specific situations such as exercise, hot weather conditions, increased fluid losses (e.g. when there is fever, vomiting or diarrhea).

3.2 Macronutrients

- **Table 3** summarizes the recommended energy, protein, fat and carbohydrate intake in CF.

3.3 Micronutrients, minerals and trace elements other than vitamins

3.3.1 Sodium

- Daily salt intake for adult CF patients should be about 4'000 to 6'000 mg NaCl which is 2-3 times more than for a non-CF adult.
- Supplementation should be considered in high risk patients (fever, exercise, hot weather) or when the intake of salt is reduced (illness with poor appetite). **The loss of sodium can be increased by 10 times during exercise in hot climates**.

Table 3: Summary of recommended daily intake in CF

	Recommended daily intake	Comments
Energy-calories*	110-200% compared to a healthy population of the same age (namely 30 kcal/kg/day)	Goal: normal BMI
Proteins	1.2-1.5 g/kg/day	Depending on the degree of malabsorption, pancreatic enzyme supplementation and chronic inflammation, the target for protein intake is ≥ 20% compared to a healthy population of the same-age.
Fat*	35-40% of total energy intake	
Carbohydrates	40-45% of total energy intake	In diabetic patients, reduction of carbohydrates intake is **not** recommended (rather the insulin dose should be adapted).
Fluids	≥ 35-45 ml/kg	To be increased in case of excessive loss (fever, exercise, hot weather conditions, vomiting, diarrhea)
Sodium	4'000-6'000mg of NaCl (1 teaspoon of salt ≅ 5'000 mg of NaCl ≅ 2'000 mg of Na ≅ 85 mmol of Na) Maximum intake 8'000 to 12'000 mg	Increase salty food intake if more salt is needed or use NaCl slow release pills or rehydration solution **(Table 4).**
Calcium	950-1000 mg	≥ 3 dairy portions/day **(Table 5)**

*The introduction of a high-calorie, high-fat diet as the standard of care in CF is considered one of the major turning points in the history of CF leading to improved survival

- In adult CF patients, the ESPEN guidelines recommend to compensate for sodium loss by increasing salty food intake. Rehydration solutions or supplemental NaCl **(Table 4)** can also be used in situations associated with increased sodium loss.
- The ESPEN guidelines propose to determine NaCl needs for supplementation by calculating the fractional excretion of sodium (FENa) with a target between 0.5% and 1.5% or simply by calculating the urinary Na:creatinine ratio (17-52mmol/mmol) which correlates to FENa. FENa has been used for children and is obviously not very useful on a daily basis. However, in case of severe salt depletion in adults, FENa may be used to better adjust salt replacement.

3.3.2 Calcium

- Lack of calcium may be due to insufficient calcium intake, low absorption because of vitamin D deficiency and/or fecal losses.

Table 4: Examples of salt supplementation and rehydratation solutions available in Switzerland

Normolytoral® 1 bag powder	Sodium chloride (350 mg) Citrate of sodium dihydrate (590 mg) Potassium chloride (300 mg) Glucose (4 g)*	1 bag in 200ml of water, 1-20x/day
Elotrans® powder 1 bag powder	Sodium chloride (700 mg) Citrate of sodium dihydrate (590 mg) Potassium chloride (300 mg) Glucose (4 g)*	1 bag in 200ml of water, 1-10x/day
NaCl caps	Sodium chloride (500 mg)	1-4caps/day

1 teaspoon of salt ≅ 5'000 mg of NaCl ≅ 2'000 mg of Na ≅ 85 mmol of Na
*Intestinal sodium transport is stimulated by the presence of glucose (sodium-glucose co-transport)

- Serum calcium is not a good predictor of calcium deficiency as 99% of calcium stock is located in the bony skeleton. Therefore, **evaluation of calcium intake** is recommended annually.
- The European Food Safety Authority recommends a calcium intake of 950-1000 mg calcium/day and the Swiss Society of Nutrition the consumption of at least 3 dairy portions/day (**see also Chapter "*Bone disease*"**).
- **Table 5** gives some examples of the calcium content of different dairy portions.

3.3.3 Magnesium

- Hypomagnesemia may develop due to:
  - insufficient intake
  - poor intestinal absorption because of exocrine pancreatic insufficiency and/or use of PPIs
  - hyperglycemia with excessive urinary magnesium excretion and
  - some medications which increase renal loss of magnesium such as thiazide diuretics, bisphosphonates, calcineurin inhibitors and aminoglycosides. Cases of tetany associated to hypomagnesemia have been described following high doses of aminoglycosides.

Table 5: Calcium content of different dairy portions (based on the Swiss Society of Nutrition)*

Type of food	Volume/weight	Calcium (mg)
Whole/drink milk	200 ml	240
Yoghurt	180 g	252
Hard cheese	30 g	273
Soft cheese	60 g	264

* See also http://www.sge-ssn.ch/media/Etage_lait_produits_laitiers.pdf

- Blood levels are not representative of the body storage of magnesium, because the major amount of magnesium is in the muscles and the bone.
- Low magnesium may contribute to muscle cramps and to delayed bowel transit time.

3.3.4 Selenium

- Selenium is part of the active site of glutathione peroxidase which has important antioxidant activity. Lack of selenium can affect muscle function and result to cardiopathy. However, **because of a narrow therapeutic range, supplementation in selenium is not recommended.**
- Reference values for daily nutritional intake of selenium established by the DACH (Societies of Nutrition from Germany, Austria and Switzerland) for non-CF adult individuals is between 60-70 μg.
- Multivitamin preparations designed for CF may contain supplementation in selenium. For example, one pill of DEKA's softgel contains 75 μg of selenium.

3.3.5 Zinc

- Zinc plays an important role in various enzymes. Zinc deficiency is associated with growth retardation, increased susceptibility to infections, delayed sexual maturation and eye problems.
- Its absorption depends on exocrine pancreatic function and the use of PERT.
- Plasma levels of zinc are of limited interest because of their large variability.
- The ESPEN guidelines recommend supplementation for patients at risk, particularly those with vitamine A deficiency and steatorhea (25 mg/day during 6 months)**.**
- One pill DEKA's softgel contains 10 mg zinc sulfate. Other preparations available in Switzerland are listed in **Table 6**.

3.3.6 Iron

- Iron not only plays an essential role in oxygen binding but it is also involved in many enzymatic activities and is necessary for cognitive function. In CF, it is also related to the severity of lung disease.
- Iron deficiency is very common. Multiple causes of iron deficiency may exist in CF: malabsorption, inflammation, chronic infection, insufficient intake (e.g. calcium inhibits iron absorption) and blood losses. If not compensated, iron deficiency will progress to hypochromic microcytic anemia.

Table 6: Examples of zinc supplementation available in Switzerland

Name/Type/Dosage	Active ingredient	Daily posology
ZINK BIOMED® 20 mg cpr pell	Zinc gluconate	1-2 coated tablets
ZINC BURGERSTEIN® cpr 30 mg	Zinc gluconate	1 coated tablet

- As ferritin is an acute phase protein, its blood levels are not easy to interpret in CF (it may be normal even when the iron stores are depleted). Only serum transferrin receptors are not influenced by inflammation and may be a more appropriate marker to detect iron deficiency. However, this test is not easily available.
- If anemia occurs, then measurements of total iron level, ferritin, or transferrin saturation are proposed to characterize the type of anemia **(Table 7)**.
- The ESPEN guidelines suggest to measure iron levels annually and, if they are low, to complete with another analysis to determine the cause of anemia (iron deficiency vs chronic inflammation). Supplementation is recommended if the deficiency persists despite the treatment of the inflammatory state **(Table 8)**. However, nowadays, free iron level is considered obsolete as it does not represent total iron storage.
- Iron deficiency without anemia may also be symptomatic (fatigue, hair loss) and should be treated. Therefore, in the presence of a low ferritin (< 30 μg/ml) and low MCV despite normal hemoglobin (Hb), some centers recommend to supplement with iron preparations, especially liquid formulas as they are better tolerated. The effect of this supplementation should be evaluated after 3 months and the treatment readapted accordingly.
- In CF patients not tolerating oral forms of iron, intravenous ferric carboxymaltose **(Table 8)** may be considered but with caution:
  - *Pseudomonas aeruginosa* can acquire iron from the host and its survival depends on iron accessibility from the environment. Six per cent of transcribed genes of *P. aeruginosa* are iron-responsive. Iron also plays a role in biofilm formation.
  - For different reasons including epithelial leakage, iron accumulates in CF airways and is present in micromolar concentrations.

Table 7: Differential diagnosis between different types of anemia (adapted from [6])

Test	Iron deficiency	Iron deficiency anemia	Anemia of chronic inflammation	Both forms of anemia
Hemoglobin (N: F >120, M>130 g/l)	Normal	Low	Low	Low
MCV (N: 80-95 fl)	Normal	<80	Low-normal	Low
Serum iron* (N: 10-30 μmol/l)	Low	Low	Low	Low
Serum ferritin [μg/l] (N: F 20-200, M 40-300 μg/l)		Below normal	Above normal	Varies
Transferrin saturation (>16years of age N <45%)	≥16	<16	Low-normal	Below normal
sTFR**	High	High	Low-normal	Variable

MCV: mean corpuscular volume; sTFR: soluble transferrin receptor
*Considered obsolete (see text).
**Normal values depend on the assay used

Table 8: Examples of iron monopreparations available in Switzerland*

Name/Type/Dosage	Active ingredient	Daily dose
FERRUM HAUSMANN® caps. 100 mg	Ferrous fumarate [Fe(II)]	100-300 mg
MALTOFER® cpr 100 mg liquid form 50 mg/20 drops	Ferric hydroxide-polymaltose [Fe(III)	100-300 mg for iron deficiency anemia 50-100 mg for iron deficiency without anemia
TARDYFERON® cpr 80 mg	Ferrous sulfate [Fe(II)]	80-160 mg
FERINJECT® 50 mg/ml for IV administration	Ferric carboxymaltose [Fe(III)]	Determined by Ganzoni's formula

*The IV forms of iron may occasionally result in immediate hypersensitivity reactions and for this reason administration is recommended in a healthcare setting followed by patient surveillance for at least 30 min after administration.

- Respiratory exacerbations have been reported following supplementation with intravenous iron however a causal relationship has not been proven. Although a direct comparison between IV and oral iron is not available in this regard, it has been hypothesized that a differential effect of IV vs oral iron on hepcidin may play a role. Hepcidin is a hormone that regulates iron-homeostasis and is produced by the liver. After oral administration of iron, hepcidin levels increase to reduce intestinal absorption and to keep the iron in the reticulo-endothelial system away from pathogens. In contrast, following administration of IV iron, this mechanism does not occur.

- Because of the potential negative impact of the intravenous form of iron and in the absence of clinical studies and recommendations, we prefer to administer a weekly, low dose of ferric carboxymaltose such as 200-300 mg/perfusion until the total dose is reached, instead of a single high dose. In addition, this medication should be avoided during exacerbations.
- The calculated dose of ferric carboxymaltose is based on the Ganzoni's formula:

Total iron deficit [mg] = weight [kg] × (target Hb – actual Hb) [g/dl] × 2,4 + iron stores [mg] *(for weight > 35 kg, iron stores = 500 mg)*

3.4 Fat-soluble vitamins

- Deficiency of water-soluble vitamins (folic acid, vitamin B12, vitamin C) is rare in CF. Patients with extensive resection of terminal ileum are at high risk for vitamin B12 deficiency.
- Deficiency of fat-soluble vitamins is frequent in CF patients, although it is very uncommon for adult CF patients to have obvious clinical signs in this regard. It results from pancreatic insufficiency, malabsorption and/or hepato-biliary disease. Occasionally, pancreatic sufficient patients may also suffer from fat-soluble vitamins deficiency.
- Measurement of fat-soluble vitamins A, D, E plasma levels and prothrombin time, INR (as an indirect marker of vitamin K status – see also **paragraph 3.4.4 Vitamin K**) is

recommended annualy. Supplementation of vitamins A, D, E and K should be initiated in case of deficiency.
  - The recommended daily dietary allowances for fat-soluble vitamins in CF are summarized in **Table 9**.
  - Treatment aims to correct suboptimal levels and to reach optimal biochemical values of these vitamins (according to the normal values of the laboratory).
  - Vitamin blood levels should be checked 3-6 months after dose adaptation.
- **To improve vitamin absorption, fat-soluble vitamins should be taken concomitantly with high fat food and pancreatic enzyme supplements (Tables 5, 6 and 7 and Chapter *"Exocrine pancreatic insufficiency"*).**

3.4.1 Vitamin A

- Because of decreased levels of retinol binding protein, patients suffering from CF-liver disease may be at risk of hypervitaminosis A. In these cases, in addition to serum retinol it is recommended to measure also serum retinyl binding protein and retinyl esters.
- Beta-carotene is probably safer than retinol supplementation as it is a provitamin A.
- During pregnancy, hypo- or hypervitaminosis A may be harmful for the fetus and should be closely monitored. Supplementation should not exceed 10'000 IU/day **(see Chapter *"Safety of medication use during pregnancy and breastfeeding"*)**.

3.4.2 Vitamin D

- Vitamin D deficiency is frequent in CF despite oral supplementation and contributes to a lower bone density.
- Recommendations for vitamin D supplementation are detailed in **Chapter *"Bone disease"***.

3.4.3 Vitamin E

- The most important physiological form of vitamin E is alpha-tocopherol.
- Vitamin E has anti-oxidative properties which may be important for the chronic inflamma-tion occurring in the airways of CF patients. Its level are strongly influenced by serum lipid concentration. In case of low or high lipid levels, and although not widely recommended yet, some authors suggest to target an alpha-tocopherol:total cholesterol ratio > 21 mg/mmol (5.4 mg/g).

Table 9: Recommended daily dietary allowances of fat-soluble vitamins in CF[3-5]

Vitamin A	Vitamin D	Vitamin E	Vitamin K
Retinol: 4'000 – 10'000 IU 1.2 – 3.0 mg Beta-carotene: 1'667 IU/kg (≤ 83'300 IU) 1 mg/kg (≤ 50 mg) for 12 weeks, then: 16'670 IU (10 mg)	800 – 4'000 IU 20 – 100 µg	150 – 500 IU 101 – 336 mg	5 – 10 mg

3.4.4 Vitamin K

- Vitamin K plays an important role in coagulation and possibly in bone homeostasis.
- CF-liver disease and long-term use of antibiotics may contribute to lower levels of vitamin K.
- Vitamin K serum levels are assessed directly in the clinical laboratory. However, there is not clear cutoff to assess vitamin K deficiency
  - Prothrombin time is only representative of vitamin K deficiency of the liver but not of vitamin K status and appears insufficiently sensitive to **detect** mild deficiency.
  - Measurement of serum vitamin K1, PIVKA-II (proteins induced by vitamin absence) or under-carboxylated osteocalcin are better markers of vitamin K deficiency than prothrombin time but are not available in routine clinical practice.
- Therefore, supplementation is recommended as vitamin K is not well stored and has no significant toxicity.

3.4.5 Substitution of fat-soluble vitamins

- According to the specific needs in fat-soluble vitamins, different preparations can be used. Available preparations are shown in **Tables 10 and 11**.

Table 10: Examples of vitamin A, E and K supplementation available in Switzerland (for vitamin D supplementation, see Chapter "*Bone disease*")

Name/Type	Active ingredient/Dosage
BURGERSTEIN Beta-Caroten® caps	Beta carotene – vitamin A 6 mg (10'000 IU) 15 mg (25'000 IU)
BURGERSTEIN vitamin E® caps	Alpha-tocopherol - vitamin E 100 UI (67 mg) 400 UI (268 mg)
VITAMINE E Mepha® caps	Alpha-tocopherol - vitamin E 300 mg (300 IU)
EVIT caps	Alpha-tocopherol - vitamin E 600 UI (400 mg) 800 UI (537 mg)
EPHYNAL® caps	Alpha-tocopherol - vitamin E 300 mg (300 IU)
VEDROP® solution for oral administration	Tocophersolan - vitamin E* expressed as tocopherol : 50 mg/mL = 75 IU/mL
DEKAs Aqua-E concentrate® solution for oral administration	Tocophersolan - vitamin E* expressed as tocopherol : 50 mg/mL = 75 IU/mL
KONAKION MM® solution for i.v. or oral administration	Phytomenadione – vitamin K 10 mg/ml

*Synthetic water-soluble form of vitamin E to be considered in cholestatic liver disease (delivery technology which acts like a micelle, facilitating absorption). Not available in Switzerland but could be imported.

Table 11: Multivitamin and mineral supplement (for details see https://dekasvitamins.com)

Name/Type	Active ingredient (summary)	Daily dose
DEKAs plus® softgel	Vit. A + beta-carotene : 450 + 10'000 µg (1500 + 16'667 IU) Vit. D3 : 75 µg (3000 IU) Vit. E : 101 mg (150 IU) Vit. K : 1000 µg Also contains hydrosoluble vitamins and trace elements	1-2
DEKAs plus® chewable tablet	Vit. A + beta-carotene : 450 + 5014 µg (1500 + 16'714 IU) Vit. D3 : 50 µg (2000 IU) Vit. E : 67 mg (100 IU) Vit. K : 1000 µg Also contains hydrosoluble vitamins and trace elements	1-2
DEKAs Essential® Capsule	Vit. A + Beta-carotene: 150 + 900 µg (500 + 1500 IU) Vit. D3 : 50 µg (2000 IU) Vit. E : 101 mg (150 IU) Vit. K : 1000 µg	1-2
Supradyn Energy	Vit. A (retinol palmitate): 2666 IU Vit. D3 : 200 IU Vit. E : 10 mg (15 IU) Vit. K : 30 µg Also contains hydrosoluble vitamins, trace elements and minerals	1
Supradyn Vital 50+	Vit. A (retinol palmitate): 1333 IU Vit. D3 : 200 IU Vit. E : 15 mg (22 IU) Does not contain Vit. K Also contains hydrosoluble vitamins, trace elements and minerals	1

- AquaDEK's®, a preparation of all fat-soluble vitamins specially intended to cover the needs of CF patients, is no longer available. It has been replaced by DEKA's® **(Table 11)**.

3.2 Oral nutritional supplements

- There are many varieties of oral nutritional supplements regarding taste (sweet or salty), the amount of calories (1 or 2.4 kcal), the protein content (6 to 20 g) and the presence or absence of fibers. All are gluten-free **(see Table S1 of the supplement).**

- To choose the ideal oral nutritional supplement, energy needs, fiber and protein requirements should be considered. In general, a high-energy nutritional supplement is proposed as a first choice.
- Fibers are useful especially in bowel transit disorders such as constipation or diarrhea.
- Supplements rich in proteins are used in cases of protein loss (e.g. infection, wounds, important digestive losses).

3.3 Enteral nutrition

3.3.1 General considerations

- Enteral nutrition (EN) should be considered when the patient's overall needs are not sufficiently covered by oral nutrition. It should be used in combination with oral nutrition when possible, or alone when oral nutrition is no longer possible.
- Enteral feeding is always preferred to parenteral nutrition as it is associated with less complications (such as infections). Parenteral nutrition should be considered when the EN covers less than 60% of the needs.
- Enteral nutrition can be provided by transnasal tubes (either nasogastric or nasojejunal), percutaneous endoscopic gastrostomy (PEG), percutaneous radiologic gastrostomy (PRG), surgical gastrostomies (GT) or percutaneous endoscopic gastrostomy with jejunal extension (PEG-J).
- **Figure S1** of the supplement provides some examples of materials used for enteral nutrition.

3.3.2 Technical aspects

- In CF patients requiring long-term enteral nutrition (>4 weeks), the establishment of a PEG or a PEG-J is preferred. Indications and contraindications are summarized in **Table 12.** Details about the care of transnasal tube, PEG and PEG-J are available in **Table S2 of the supplement.**
- Dieticians should assess the needs and the risks of undernutrition / dehydration of the patient and determine the daily target caloric intake (**Tables 3 and 9)**.
- High energy polymeric formulas (containing mostly intact nutrients and requiring intact digestive function), with or without fiber, should be preferably chosen, in addition to a multivitamin supplement with or without trace elements.
- Administration of the nutrition should always be carried out via a pump to ensure a continuous flow avoiding overfeeding and bronchoaspiration. It is usually administered overnight to allow the patient to maintain his/her autonomy and to get high-energy diet during the day. Bolus feeds can also be considered during the day in addition to nocturnal feeding.
- Special attention should be paid to the patient's digestive tolerance, depending on the type of product and its speed of administration. These aspects need to be discussed with the dieticians.
- A raised position of the trunk at 30° is recommended during EN to avoid gastroesophageal reflux and bronchial aspiration.

Table 12: Indications and contraindications for transnasal tube, PEG et PEG-J

	Indications	Contraindications
Transnasal tube	Inability to meet short-term nutritional needs	Nasal polyposis Long term (>4-6 weeks) EN
PEG **PRG**	Inability to meet long-term nutritional needs Neurological swallow impairment Upper gastrointestinal tract neoplasm Trauma Patients with long-term ventilation Perioperative period in oropharyngeal surgery	Severe coagulation disorders Parietal inflammation, infectious or neoplasia Cancer or gastric wall pathology Adherence or intraperitoneal carcinomatosis Gastrointestinal fistulas
PEG-J	Gastric emptying disorders Risk of aspiration pneumonia Gastric Decompression Pyloric stenosis Duodenal stenosis	

EN: enteral nutrition, PEG: percutaneous endoscopic gastrostomy, PEG-J: percutaneous endoscopic gastrostomy with jejunal extension, PRG: percutaneous radiologic gastrostomy

- PERT and enteral nutrition:
  - Pancreatic enzyme replacement is usually given at the beginning and the end of the feed. At a low rate of infusion, enzyme requirements are usually low.
  - Regarding dosing requirements of PERT during enteral nutrition: important variations exist and dose should be individualized depending on patient needs and symptoms. Usually the starting dose is 1'000 IU of lipase per gram of fat provided by the enteral nutrition but doses may range between 500-4000 IU of lipase per gram of fat or 25'000-50'000 per meal (in case of bolus feeds).
    - When possible, pancreatic enzymes capsules should be swallowed. For patients who have difficulty swallowing capsules, it is possible to open them and take their content mixed with food or drink at a pH <5.5 (e.g. applesauce or yoghurt, apple, orange or pineapple juice).
    - The microgranules contained in the capsule are gastro-resistant. Thus, they should not be chewed or crushed, otherwise the efficacy of pancreatic enzymes would be lost in the gastric acidic environment.
    - Administration of PERT through a gastrotomy feeding tube is problematic due to the risk of tube obstruction. Dissolution of microgranules in sodium bicarbonate solution before use is one of the proposed approaches (the solution should be prepared just before use, the volume frequently used is 10-20 ml sodium bicarbonate solution 8.4%). Dosage adjustment may be necessary to compensate some loss of enzyme activity.
    - Feeding should be stopped during administration of PERT through the tube.

- In case of diarrhea additional adaptation may be needed (type of nutrition, flow of infusion, PERT).
- Different products are commercially available and should be discussed with the clinical nutrition team. A regular control of laboratory values is important after the introduction of enteral nutrition to prevent the refeeding syndrome.

3.4 Refeeding syndrome

- Refeeding syndrome may occur in malnourished patients upon reintroduction of enteral or parenteral nutrition. It is characterized by phosphate, potassium and magnesium imbalance but glucose, sodium and water shifts contribute also to the high morbidity and mortality associated with this disorder.
- During a long duration of starvation, ketones and free fatty acids become the major source of energy to prevent muscle catabolism. If this state persists, catabolism and loss of lean body mass will occur and is associated with depletion of intracellular phosphate and various vitamins including thiamine.
- During refeeding, carbohydrate reintroduction leads to increased levels of insulin which induce biochemical changes such as important intracellular shift of potassium, phosphate and water. In addition, glucose metabolism is altered leading to metabolic acidosis, ketoacidosis and hyperosmolar states.
- Patients will therefore suffer from cardiac, respiratory, renal, neurological, gastrointestinal, musculoskeletal and hematological consequences of hypophosphatemia, hypokalemia, hypomagnesemia, hypocalcemia and hypovitaminosis (such as B1 hypovitaminosis).
- It is therefore crucial to identify patients at risk for refeeding syndrome. Nice criteria have been established to detect such patients **(Table 13)**. Nutrition reintroduction in patients at risk for refeeding syndrome must be performed in close collaboration with the nutrition team. Biological and clinical monitoring is required during this delicate phase.

Table 13: Nice criteria[2]: patients at high risk for refeeding syndrome

Patient has one or more of the following:
BMI less than 16 kg/m^2
Unintentional weight loss greater than 15% within the last 3–6 months
Little or no nutritional intake for more than 10 days
Low levels of potassium, phosphate or magnesium prior to feeding
Or patient has two or more of the following:
BMI less than 18.5 kg/m^2
Unintentional weight loss greater than 10% within the last 3–6 months
Little or no nutritional intake for more than 5 days
History of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics

4. SPECIAL SITUATIONS

4.1 Pregnancy

- Counseling before conception should be offered to all CF women.
- Reassess fat-soluble vitamin levels to avoid excessive dosages (notably of vitamin A).
- Supplementation of folic acid (0.4mg/day) is recommended for all pregnant women.
- Increasing the frequency of monitoring is recommended during pregnancy, with a close follow-up after delivery.
- Nutritional needs rise during breastfeeding. Therefore, nutritional status should be reassessed following delivery in CF women at risk for undernutrition. Breastfeeding may have to be interrupted in this case.
- If the lactating woman is diabetic, she is at risk for hypoglycemia.
- Information about gestational diabetes screening is provided in **Chapter "*CF-related diabetes*".**

4.2 CF-related diabetes (see also Chapter "CF-related diabetes")

- CF patients newly diagnosed with CF-related diabetes should continue to get high energy diets and should not be encouraged to reduce their consumption of carbohydrates. Instead, close glucose level monitoring is advised in order to adjust insulin needs.

5. SUMMARY

- **Figure 3** provides an algorithm for nutritional intervention in CF

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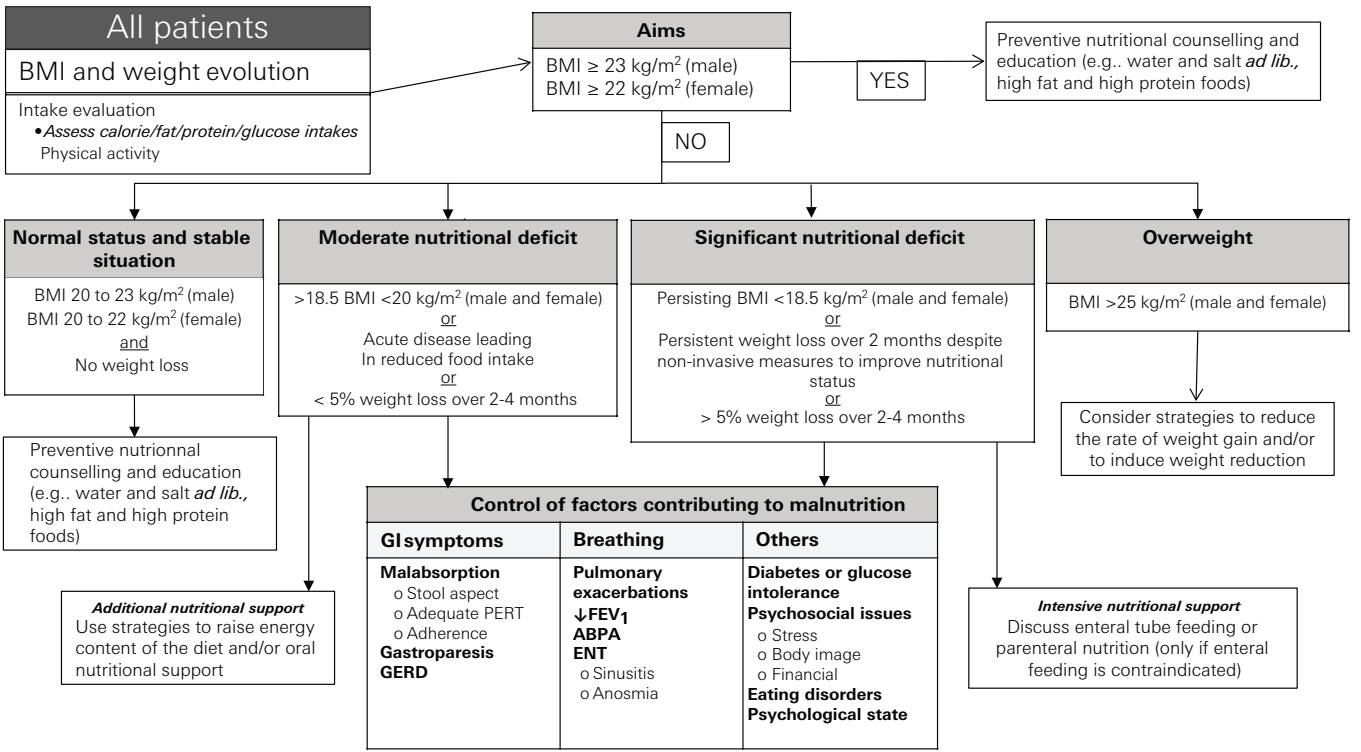
Figure 3: Algorithm for nutritional intervention in CF (adapted from [4,5,7])



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S6.7 Nutrition

Table S1: Examples of oral nutritional supplements available in Switzerland

Name	Company	Quantity (ml)	Kcal	Protein (g)	Caracteristics	Flavor
Ensure Plus	Abott SA	200	300	12.5	High energy, fiber-free, normal protein, gluten-free, virtually lactose-free	Fruits of the forest, Strawberry, Raspberry, Coffee, Chocolate, Banana, Vanilla
Ensure Plus Advance	Abott SA	220	330	20	High energy, enriched fiber, high protein, gluten-free, low lactose	Peach, Pinacolada
Ensure TwoCal	Abott SA	200	400	16.8	High energy, fiber-free, normal protein, gluten-free, virtually lactose-free	Vanilla, Banana, Strawberry
Fresubin Energy Drink	Fresenius Kabi	200	300	11.2	High energy, fiber-free, normal protein, gluten-free, virtually lactose-free	Cappuccino, Cassis, Vanilla, Strawberry, Exotic fruits
Fresubin 2 kcal Drink	Fresenius Kabi	200	400	20	High energy, enriched fiber, high protein, gluten-free, low lactose	Fruits of the forest, Vanilla, Nature, Apricot-peach
Fresubin Protein Energy Drink	Fresenius Kabi	200	300	20	High energy, high protein, gluten-free, virtually lactose-free	Chocolate, Vanilla, Wild strawberry, Hazelnut, Cappucino, Tropical fruits
Resource Energy	Nestlé	200	300	11.2	High energy, fiber-free, normal protein, gluten-free, low lactose	Vanilla, Apricot, Chocolate, Strawberry-raspberry, Coffee, Banana

(continued)

Resource 2.0 Fibres	Nestlé	200	400	18	High energy, enriched fiber, high protein, gluten-free, low lactose	Vanilla, Apricot, Fruits of the forest, Nature, Coffee, Strawberry, Chocolate
Resource Protein	Neslté	200	250	18.6	High energy, high protein, gluten-free, virtually lactose-free	Vanilla, Apricot, Fruits of the forest, Strawberry
Fortimel Energy	Nutricia	200	300	12	High energy, normal protein, gluten-free, lactose-free	Strawberry, Banana, Chocolate, Vanilla
Fortimel Protein	Nutricia	200	480	29	High energy, high protein, gluten-free, low lactose	Vanilla, Moka, Banana, Strawberry, Red Fruits, Peach-mango, Mutlifruits
Fortimel Energy Multi Fibre	Nutricia	200	308	12	High energy, enriched fiber, normal protein, gluten-free, virtually lactose-free	Vanilla, Chocolate, Strawberry

Proposed approach when using enteral feeding

- Wash hands before and after handling.
- Administer only still water (no acidic beverages).
- Unblock the probe, if necessary, with carbonated water (preferably) or coca beverage (may color the probe) using a 10 ml syringe.
- Check the position of the probe by removing some gastric fluid.
- Rinse before and after feeding.
- Rinse before, between each medication and after each medication.
- Monitor patient's fluid balance, perform input-output assessments if necessary.
- Replace tubing every 24 hours.
- Clean the tip of the probe with hot water and possibly with a new toothbrush.
- Stoma care daily.
- If the ostomy is not used, rinse it once a day with 20 ml of water.

- Track whether the target caloric coverage is reached (weight, consultation by dietician).
- Pain should be carefully evaluated but usually resolves within a few days. Mild analgesics are sufficient most of the time.
- Diarrhea can occur if the nutrition is too cool or open for >24h before usage. If diarrhea continues discussion with the dieticians is required to adapt the nutrition (type of nutrition, flow of infusion, PERT).
- Insertion point: should be regularly checked for redness, chemical burns on effluent regurgitation/nutrition, granulation, eschar.
- If necessary, disinfection with a non-alcoholic and non-colored antiseptic.
- In case of fever medical advice should be sought.
- Ensure that the patient has access to a psychological support as body image change may have a psychological impact.

Table S2: Enteral nutrition devices and their specific care

Feeding tube	Tubes and set up	Specific care	Precautions/ complications
Transnasal tube	• Small diameter probes (Freka®, Bengmark®), more likely to get clogged. • In general, these probes are positioned to the gastric level, if necessary, they can be moved to the jejunal level. • Post-implementation X-ray to ensure proper placement. • This probe is attached to the nose and the cheek.	• Always prefer medications in liquid form. Administer one drug at a time and rinse well with 20 cc of tap water. Always rinse between 2 drugs to avoid precipitation. • A pen mark will identify the exit of the probe at the nose and will allow to verify that it remains in place.	• In CF patients, recurrent cough can cause migration of the tube in the airways. • Change the location of the fixation of the extremity of the probe every day to reduce the risk of pressure ulcers and of nasal bleeding. • It may be associated with nausea, vomiting, gastro-esophageal reflux, sleep disturbance. • If the EN is planned for a long-term, a percutaneous gastrostomy should be considered early.

(continued)

PEG (Percutanuous Endoscopic Gastrostomy)	• The feeding tube is inserted through the abdominal wall and into the stomach. It is placed under endoscopic guidance, usually under general anesthesia. • A collar allows to attach the probe to the gastric wall, while a fin or a washer allows to maintain the device on the skin. • At the end of the procedure, the probe is put under tension and under a bandage.	• The operator should take care of the first change of the bandage and the first mobilization of the tube (starting on day 6) to allow the adhesion of the digestive wall to the skin and to avoid the risk of peritoneal passage of the EN. • From day 6 to day 16, sterile bandage and probe mobilizations should be done daily. • From day 16, as a general rule, the probe is kept in the air and mobilizations continue at the same pace. This mobilization should be done, after having released the probe of the device which keeps it in tension with the skin. • For PEG with fin, repair kits allow the replacement of all or part of the broken externalized device.	• Unless there is a contraindication, the tube can be safely used 3 to 6 hours after insertion. Sterile saline should be infused first to evaluate the permeability of the system (intra peritoneal infiltration would cause severe pain). Mobilization: • Back and forth at least 1 to 2 cm to avoid impaction of the collar in the gastric mucosa (this may lead to loss of permeability of the PEG and partial gastrectomy). • Rotation of the probe from 90 to 180° to avoid pressure sores. It is recommended to make these rotations always in the same direction (defined at the beginning) to keep as much as possible the same diameter and the symmetry of the ostomy (limiting the risks of regurgitation of gastric juice and diet on the cutaneous plane and associated dermatitis).

(continued)

			• Once mobilization is complete, the probe will be re-tensioned gently when it is reattached to the fin or the washer. • When the device contains a washer, the strength of the fixation may decrease over time: the tension should be checked regularly. • PEG may be left in place for 4 weeks to several years, but in the long-term the transition to a gastric tube (the collar that fixes the probe to the gastric wall is replaced by a balloon filled with water) or a gastrostomy button should be considered as they are more convenient for the patient. In these cases, the PEG is first removed endoscopically. • Patients may complain of post-insertion pain • Leakage and infection at the site of gastrostomy may occur and need topical treatment (antibiotic, steroid)

(continued)

PRG (Percutaneous Radiologic Gastrostomy)	• The feeding tube is directly inserted through the abdominal wall into the stomach under CT scan or ultrasound guidance (to avoid penetration through the colon if interposed). • Previous pigtail tubes have been increasingly replaced by gastric tubes.	If a gastric tube has been placed: • The operator should take care of the first change of sterile bandage starting day 6. • From day 6 to day 15, daily cleaning with 0.9% NaCl and disinfection with aqueous disinfectant without dye followed by sterile bandage. • At day 15, as a general rule, the probe should be kept in the air and mobilization should continue at the same pace. This mobilization will be done, after having released the probe of the device which keeps it in tension with the skin. • Sutures are removed on day 15 (or according to medical order) and then daily mobilization should begin.	• Unless there is a contraindication, the tube can be safely used 3 to 6 hours after insertion. Sterile saline should be infused first to evaluate the permeability of the system (intra peritoneal infiltration would cause severe pain). • The balloon of the gastric tube needs to be checked regularly to ensure it remains well sealed (the quantity of water to introduce may vary according to the gastrostomy model but is kept the same until the change of the device). • An advantage of the gastric tube is that it can be changed by the patient or a caregiver. • **In case of loss or untimely tearing of the device, a new gastric tube must be reinserted within 6 hours (otherwise the ostomy may close spontaneously).** The patient should be strongly advised to carry on him a spare device. • Patients may complain of post-insertion pain.

(continued)

			• Leakage and infection at the site of gastrostomy may occur needing topical treatment (antibiotic, steroid).
PEG –J or PEJ (percutaneous endoscopic gastrostomy with jejunal extension)	• If needed a PEG can be extended to the jejunal level.	• **Tube rotations are proscribed because of the risk of probe dislocation.** • Mobilization of the tube (small movements back and forth) should be performed daily from day 6 with much caution to avoid dislodgement from the jejunum.	• A gastric tube or a gastrostomy button cannot be extended to the jejunum • As with all jejunal feeding routes, never aspirate (no gastric residue).
Surgical jejunostomy	• The tube is surgically inserted into the jejunum after the ligament of Treitz.	• No mobilization of the device should be performed.	• As with all jejunal feeding routes, never aspirate (no gastric residue).