Cystic Fibrosis our focus

Nutritional Management of Cystic Fibrosis

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Fighting for a Life Unlimited

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Nutritional management of cystic fibrosis

Index

Foreword

1.0 Introduction

1.1 Factors associated with poor nutrition
- 1.1.1 Increased stool energy losses due to fat malabsorption
- 1.1.2 Increased energy requirements of CF
- 1.1.3 Reduced oral energy intakes
- 1.1.4 Other factors

1.2 Nutritional challenges

1.3 CF specialist care

1.3 Can nutrition be improved?

1.4 References

2.0 Nutritional assessment and growth

2.1 Introduction

2.2 Methods of nutritional assessment
- 2.2.1 Head circumference or occipital-frontal circumference
- 2.2.2 Weight
- 2.2.3 Height
- 2.2.4 Body mass index (BMI)
- 2.2.5 Puberty
- 2.2.6 Recording and monitoring growth and nutritional status
- 2.2.7 Standard deviation scores

2.3 Assessment of body composition

2.4 Good practice points
- 2.4.1 Infants and children
- 2.4.2 Adults

3.0 Nutritional management strategies

3.1 Introduction

3.2 Factors compromising dietary and energy intakes
- 3.2.1 Appetite
- 3.2.2 Knowledge
- 3.2.3 Other factors

3.3 Dietetic management
- 3.3.1 Good practice points

3.4 Preventative nutritional advice
- 3.4.1 Feeding infants, toddlers and young children
- 3.4.2 Infants
- 3.4.3 Sodium supplementation in infants
- 3.4.4 Gastro-oesophageal reflux (GOR) in infants
- 3.4.5 Weaning/introduction of solids and feeding toddlers
- 3.4.6 Behavioural intervention
- 3.4.7 School age children
- 3.4.8 Adolescents/adults
- 3.4.9 Good practice points

3.5 Moderate nutritional deficit
- 3.5.1 Improving Growth and Nutritional Status
- 3.5.2 Infants
- 3.5.3 Improving the energy content of the diet – all ages
- 3.5.4 Good practice points

3.6 Oral nutritional supplements (ONS)
- 3.6.1 Good practice points

3.7 Significant nutritional deficit
- 3.7.1 Enteral tube feeding (ETF)
- 3.7.2 Route of feeding
- 3.7.3 Nasogastric (NG) feeding
- 3.7.4 Gastrostomy feeding
- 3.7.5 Feed administration
- 3.7.6 Types of feed
- 3.7.7 Pancreatic enzyme replacement therapy and enteral tube feeds
- 3.7.8 Monitoring
- 3.7.9 Good practice points

3.8 Appetite stimulants

3.9 Anabolic agents

3.10 Parenteral nutrition (PN)

3.11 Good practice points

4.0 Pancreatic enzyme replacement therapy

4.1 Introduction

4.2 Determination of pancreatic status

4.3 Recommendations for commencing PERT
- 4.3.1 Infants
- 4.3.2 Older children and adults

4.4 Pancreatic sufficiency

4.5 Selection of type of PERT

4.6 Dosage recommendations to optimise efficacy of PERT
- 4.6.1 Dosage recommendations to ensure safety of PERT

4.7 Practical administration of PERT
- 4.7.1 Infants
- 4.7.2 Children and adults
- 4.7.3 Efficacy of PERT
- 4.7.4 Practical advice

4.8 Administration of PERT via feeding tubes

4.9 Atypical presentations

4.10 Good practice points

5.0 Vitamins and minerals

5.1 Introduction
5.2 Vitamin A
- 5.2.1 Signs and symptoms of deficiency
- 5.2.2 Toxicity
- 5.2.3 Monitoring
- 5.2.4 Supplementation
- 5.2.5 Good practice points

5.3 Vitamin D
- 5.3.1 Signs and symptoms of deficiency
- 5.3.2 Monitoring
- 5.3.3 Good practice points

5.4 Vitamin E
- 5.4.1 Signs and symptoms of deficiency in CF
- 5.4.2 Toxicity
- 5.4.3 Monitoring and supplementation
- 5.4.4 Good practice points

5.5 Vitamin K
- 5.5.1 Signs and symptoms of deficiency
- 5.5.2 Monitoring
- 5.5.3 Supplementation
- 5.5.4 Good practice points

5.6 Water-soluble vitamins
5.7 Sodium
- 5.7.1 Monitoring
- 5.7.2 Supplementation
- 5.7.3 Good practice points

5.8 Calcium
- 5.8.1 Recommendations
- 5.8.2 Assessment of status
- 5.8.3 Guidance on high intakes
- 5.8.4 Good practice points

5.9 Magnesium
- 5.9.1 Magnesium supplementation
- 5.9.2 Good practice points

5.10 Zinc
- 5.10.1 Signs and symptoms of deficiency
- 5.10.2 Monitoring
- 5.10.3 Supplementation
- 5.10.4 Good practice points

5.11 Iron
- 5.11.1 Assessment of status
- 5.11.2 Supplementation
- 5.11.3 Good practice points

5.12 Antioxidants
- 5.12.1 Supplementation
- 5.12.2 Good practice points

5.13 Essential fatty acids
- 5.13.1 Good practice points

5.14 Probiotics
- 5.14.1 Good practice points

6.0 Nutritional challenges

6.1 Care of infants presenting with meconium ileus (MI)
- 6.1.1 Good practice points

6.2 End-stage nutritional support
- 6.2.1 Good practice points

6.3 Overweight and obesity
- 6.3.1 Good practice points

6.4 Body image and disordered eating behaviour
- 6.4.1 Good practice points

6.5 Nutrition and pregnancy
- 6.5.1 Special considerations
- 6.5.2 Good practice points

6.6 Lung Transplantation
- 6.6.1 Pre-transplant
- 6.6.2 Good practice points
- 6.6.3 Post-transplant
- 6.6.4 Good practice points

6.7 Sports nutrition
- 6.7.1 Good practice points

7.0 Co-morbidities

7.1 Bone health
- 7.1.1 Risk factors
- 7.1.2 Monitoring
- 7.1.3 Prevention and treatment
- 7.1.4 Good practice points

7.2 Cystic fibrosis-related diabetes (CFRD)
- 7.2.1 Monitoring
- 7.2.2 Treatment
- 7.2.3 Good practice points

7.3 Constipation
7.4 Distalintestinal obstruction syndrome (DIOS)
- 7.4.1 Good practice points

7.5 Liver disease
- 7.5.1 Good practice points

7.6 Renal disease
7.7 Gastro-oesophageal reflux disease (GORD)
- 7.7.1 Risk factors
- 7.7.2 Monitoring
- 7.7.3 Treatment

8.0 References

Foreword

This document has been developed to update the previous guidelines on the Nutritional Management of Cystic Fibrosis (Cystic Fibrosis Trust, 2002). This is a comprehensive support document for dietitians working with infants, children and adults with cystic fibrosis (CF).

The Nutrition Consensus Working Group recognises that practice may differ between Specialist CF Centres and between paediatric and adult care; this document represents what the current Nutrition Consensus Working Group and those who have contributed to the document consider to be best clinical practice.

The endorsement process of the document by the Cystic Fibrosis Trust has included reviews by relevant experts in addition to peer reviews.

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1.0 Introduction

Continued medical and nutritional advances in treatment and detailed attention to the nutritional management of people with CF have led to an ageing CF population. The median predicated survival in the UK in 2014 was 40.1 years, with 59.3 percent of the CF population being over 16 years of age.[1]

Nutritional management is an essential part of multidisciplinary care for children and adults with CF. Despite ongoing nutritional challenges from diagnosis, the main goals of nutritional management are to achieve normal growth, development and nutritional status and to maintain this throughout life. Since 2007 all babies born in the UK are screened for CF as part of the National Newborn Screening Programme; this enables the earlier introduction of treatment, thus maximising the potential to optimise nutritional status.[2–4]

All people with CF require close and regular evaluation of growth, nutritional status and body composition throughout their lives. Reliable and sequential measurements of growth and nutritional status are an essential part of the clinical assessment of health status in CF. Regular assessment with a specialist CF dietitian will help to ensure that any deterioration or deviation in nutritional status is detected early, so that nutrition interventions can be initiated. Poor growth and malnutrition contribute to increased mortality and morbidity in CF and have a long-term impact on lung function.[5–11]

A high-fat, high-energy diet has been a standard part of the nutritional management of CF for the past 35 years. This approach has resulted in improved nutritional status and survival. Although many people with CF who are pancreatic insufficient should be able to achieve a good nutritional status by following a high-fat, high-energy diet with adequate pancreatic enzyme replacement therapy (PERT), malnutrition is still a concern in some people with CF. Early recognition of faltering growth, poor nutrition or weight loss is therefore vital.

People with CF who are pancreatic sufficient (PS) generally have lower energy requirements and fewer nutritional problems than those who are pancreatic insufficient (PI). Recently, with modern management of CF, overweight and obesity have become a problem for some.[12,13] This group will need advice to adopt healthier eating principles in order to lose weight or prevent further weight gain.

1.1 Factors associated with poor nutrition

Energy requirements vary widely in CF and are dependent on age, gender, nutritional status, lung function, clinical status and presence of pancreatic insufficiency. Due to the high degree of variability in energy requirements it is important that nutritional needs are assessed on an individual basis taking these factors into account. Energy requirements are now quoted to be 110–200 percent of those required by healthy individuals of the same age and gender.[7]

Poor nutrition in CF results from an unfavourable energy balance due to a number of interlinked factors:

- Increased stool energy losses due to fat malabsorption
- Increased energy requirements of CF related to disease severity
- Reduced oral energy intake
- Other factors

1.1.1 Increased stool energy losses due to fat malabsorption

Thickened secretions in the gastrointestinal tract cause the exocrine ducts of the pancreas to become blocked; this inhibits the secretion of pancreatic enzymes into the gastrointestinal tract. Untreated pancreatic insufficiency results in maldigestion and malabsorption of fat and to a lesser extent protein, contributing to sub-optimal nutritional status and deficiency of fat soluble vitamins. Current UK CF Trust Registry data shows 84 percent of the CF population are taking pancreatic enzyme replacement therapy (PERT) to control the symptoms of maldigestion and malabsorption.[1]

Reduced pancreatic bicarbonate secretion, increased gastric acid secretion, reduced bile acid secretion and abnormal gastric and intestinal motility will also contribute to maldigestion and malabsorption in CF. Regular dietetic advice by an experienced CF dietitian is essential to achieve optimal PERT and hence avoid both over- and under-dosing of pancreatic enzymes. Despite PERT, maldigestion and malabsorption may still continue to contribute to increased energy losses in some people with CF (see section 4.0).

1.1.2 Increased energy requirements of CF

Infections, inflammation and worsening lung function contribute to an increase in resting energy expenditure in CF.[14,15] There may also be an adaptive response to malnutrition which results in increased protein catabolism.[16]

1.1.3 Reduced oral energy intakes

Infection related anorexia, increased sputum production, abdominal pain, gastro-oesophageal reflux, vomiting, food dislikes, eating behaviour problems, disordered eating and psychosocial problems may contribute to poor food intakes and hence energy and nutrient deficits. Some people with CF do achieve good energy intakes,[17] however many fail to meet their recommended energy requirements.[18,19] Individualised dietary advice, intervention and regular monitoring are therefore essential.

1.1.4 Other factors

Impaired glucose tolerance and the development of CF-related diabetes (CFRD) may contribute to energy losses through glycosuria. It is important that people with CF are screened annually[20] for CFRD and that diabetes management is optimised to minimise these urinary losses.

With a greater knowledge of genetics in CF there is a link between mutations associated with pancreatic sufficiency or mutations with residual CFTR function and improved nutritional status. The roles of genetic modifiers have also been identified in the influence of BMI variations in young twins and siblings with CF.[21]

Psychosocial factors and peer pressure along with media influences on the general population regarding dieting and the desire to be slim can have negative nutritional consequences for people with CF especially females.[22,23]

1.2 Can nutrition be improved?

The improvement in survival of people with CF has resulted in further nutritional challenges which include the treatment of CFRD, pregnancy, renal disease, reduced bone mineral density, transplantation, overweight and obesity.

The complex nature of the nutritional management of CF emphasises the importance of regular dietary review and assessment by a Specialist CF Dietitian from infancy and throughout life to ensure optimal nutritional status is achieved and maintained.[24]

1.3 Specialist care

In the UK, people with CF should have their care provided under the direct supervision of a Specialist CF Centre. Children may receive shared care with a Network CF Clinic or full care from a Specialist CF Centre. Due to the increasing challenges of managing CF in adulthood full care should be provided by a Specialist CF Centre, and only in exceptional circumstances should adults receive care through Network CF clinics.[24] A Specialist CF Centre will have a minimum of 100 adults or children and have a core multidisciplinary team of trained and experienced CF specialist healthcare professionals which should include a Specialist CF Dietitian.

Table 1: Recommended dietetic staffing levels[24]

	75 patients	150 patients	250 patients
Adult centre (WTE)	0.5	1.0	2.0
Paediatric centre (WTE)	0.5	1.0	1.5

Whilst these are helpful recommendations, exposure to a critical mass of patients is essential to ensure staff are experienced enough to understand the complexity of management. For example a Specialist Centre may have 0.5 WTE for 75 patients but if that 0.5 WTE comprises a number of individuals contributing 0.1 or 0.2 WTE they will be unable to develop the appropriate expertise. Incremental changes in staffing numbers do not necessarily occur with patient numbers greater than 250.[24]

The CF Trust Standards of Care[24] also make the following recommendations:

A Specialist CF Dietitian must:

- Be registered with Health and Care Professions Council.
- Be a member of the Cystic Fibrosis Dietitians' Group.
- Have specialist knowledge and be experienced in the care of children and/or adults with CF.
- Maintain CPD through attendance at study days and meetings such as national and international CF conferences.

Roles and responsibilities of Specialist CF Dietitians include:

- Providing regular dietetic support and advice to people with CF and their parents/carers in an outpatient and inpatient setting.
- Ensuring that dietetic practice is evidence-based and reflects current research, clinical guidelines and consensus views.
- Providing appropriate advice and education to people with CF and their carers on the nutritional management of CF. This should be individualised advice taking into account age, clinical and nutritional status.
- Acting as a resource on the nutritional training, development, education and support of other allied health and medical professionals working in CF.
- Taking part in dietetic and multi-professional CF research and audits.
- Evaluating clinical practice identifying improvements where necessary.

The CF Trust Standards of Care[24] also suggests that a Specialist CF Dietitian should:

- See all people with CF for a nutritional annual review (PS and PI).
- See all inpatients at least twice per week or more frequently if appropriate.
- Be available at every clinic visit and ensure all PI patients are seen at every clinic visit and those who are PS are seen as necessary.

Current Service Specification and the Commissioning for Quality and Innovation group (CQUIN) within the UK suggest that a dietitian should see all patients at every clinic visit.[25] At the time of writing these Standards of Care and Service Specifications guide CF care.

The European Cystic Fibrosis Society have published detailed Standards of Care including the Framework for the Cystic Fibrosis Centre.[26–28]

2.0 Nutritional assessment and growth

2.1 Introduction

All people with CF require close and regular evaluation of growth, nutritional status and body composition throughout their lives. Reliable and sequential measurements of growth and nutritional status are an essential part of the clinical assessment of health status in CF. Regular assessment will help to ensure that any deterioration in nutritional status is detected early, so that nutrition interventions can be initiated.

2.2 Methods of nutritional assessment

In order to gain an accurate measure of nutritional status, a variety of indicators including weight, height, head circumference (infants), body composition, dietary and biochemical measurements should be used as a basis for evaluation. Growth measurements should be consistent and performed by experienced staff. The following section gives detailed information on how growth should be monitored and how growth failure should be defined in CF. The frequency of routine measures of nutritional status depends on age and clinical status (see table 2). Standard operating procedures (SOPs) for the measurement of weight, height and head circumference are designed to gain consistency in the measurement of nutritional status in clinical trials and can be requested from the European Cystic Fibrosis Society Clinical Trials Network.[29]

2.2.1 Head circumference or occipital-frontal circumference

Head circumference is a measurement of an infant's head around its largest area. It measures the maximum distance from above the eyebrows and ears and around the back of the head. A non-stretchable disposable tape should be used for the measurement. Head circumference should be assessed in all infants at least up to the age of one year but, preferably two. Measurements should be plotted on the appropriate percentile chart.[30]

2.2.2 Weight

All people with CF should be weighed at each clinic visit and at least twice weekly throughout hospital admissions. Weight measurements should be performed using calibrated electronic weighing scales. Weight measurements should be plotted on the appropriate percentile chart up to the age of 18 years.[30] When interpreting weight factors such as ascites, oedema, hepatosplenomegaly and dehydration should be taken into consideration.

2.2.3 Height

All people with CF should have their length measured until the age of two years and then standing height measured at each clinic visit and during hospital admissions until growth has ceased. A correctly installed stadiometer or approved portable measuring device should be used to measure height. As with weight, height measurements should be plotted on the appropriate percentile chart until growth has ceased.30 A current and accurate height measurement is important at all ages as it is used for the calculation of predicted lung function. Growth may continue beyond the age of transfer to an adult centre if puberty has been delayed. Once growth has ceased, maximal attained height should be used to calculate body mass index (BMI) and lung function.

2.2.4 Body mass index (BMI)

In routine clinical practice, BMI (weight(kg)/height(m)2)31 is now accepted as the most appropriate measure of nutritional status in people with CF over the age of two years.[7,11,32] Body mass index is simple, quick and inexpensive to perform and determines whether weight is in the appropriate range for stature.

In children, BMI percentile (BMIp) position is a more sensitive marker of nutritional failure than other weight and height based measures such as percentage ideal body weight. However, BMI can mask nutritional stunting as it adjusts for height.[33–35] It is therefore important that BMI is not used in isolation to assess nutritional status in growing children. Changes in weight and height should also be considered. Body mass index cannot be used in children under the age of two years, as there are no reference values for BMIp for this age group.

In children over the age of two years a BMIp of less than or equal to the 20th percentile has been shown to be associated with reduced lung function and low bone mineral density,[36] whereas, a BMIp greater or equal to the 50th percentile is associated with better lung function.[7,37]

In adults with CF a better lung function is associated with a higher BMI; women should aim to achieve a BMI of 22kg/m2 in and men 23kg/m2.7

Table 2: Frequency of measures to assess growth and nutritional status

Measure	Infants and Children (0–2 years)	Children and Adolescents (2–18 years)	Adults (>18 years)
Head circumference (cm)	1–2 weekly until thriving then each clinic visit	N/A	N/A
Weight (kg)	1–2 weekly until thriving then each clinic visit	Each clinic visit / twice weekly during inpatient admissions	Each clinic visit / twice weekly during inpatient admissions
Length/height (cm/m)	1–2 weekly until thriving then each clinic visit	Each clinic visit	Each clinic visit until growth ceased, then annually
BMI (kg/m2)	N/A	Each clinic visit/ twice weekly during inpatient admissions	Each clinic visit / twice weekly during inpatient admissions

2.2.5 Puberty

Delayed growth and late onset of puberty can occur in CF as a result of malnutrition, severe disease or glucocorticoid therapy.[38–40] The possibility of pubertal delay, which may affect BMI, should be taken into consideration when assessing nutritional status and interpreting growth charts. Noting stages of breast, pubic hair and genital development and recording the age of menarche in girls are important in assessing the stage of development.[41] Children with delayed puberty will initially lose height percentile positions but should catch up when they enter their delayed growth spurt. Height should continue to be measured at each clinic visit until growth has ceased regardless of age. Recent studies have indicated delayed and/or attenuated peak height velocity may reduce final adult height.[42,43]

2.2.6 Recording and monitoring growth and nutritional status

All head circumference, weight, height and BMI measurements should be recorded longitudinally and in a graphical format to assist in the evaluation of changes in nutritional status. Head circumference, weight and height measurements must be corrected for gestational age in premature infants born 32 to 37 weeks gestation until one year of age and until two years of age for those born before 32 weeks gestation.

Measurements must be plotted on the appropriate percentile charts in all children with CF up to the age of 18 years or until growth has ceased. After this time nutritional status should be monitored using weight and BMI.[31]

In the UK, UK-WHO age-specific growth charts should be used.[30] There is no universally accepted cut off for malnutrition in children with CF and no single measure should be used. When interpreting height percentile charts genetic short stature and the effect of delayed puberty, both of which will lead to an over estimate of malnutrition, should be taken into consideration. Weight and height velocity charts provide greater sensitivity to the assessment if growth is poor. However, in infancy, attained weight or length has been shown to be more sensitive than velocity-based definitions for predicting subsequent diminished growth.[44]

2.2.7 Standard deviation scores

Weight, height and BMI measurements can be converted to standard deviation scores (SD scores, SDS or Z-scores). This computed measurement is used to determine the nutritional status of an individual in comparison to reference measurements of a comparable population. Thus, SD scores standardise height, weight and BMI for age and gender. Computer software programs (LMS Growth) are available to calculate SD scores.[45–47] Standard deviation scores are mainly used in research as they allow statistical analysis of linear values in longitudinal studies comparing growth between groups of patients.

2.3 Assessment of body composition

Weight and BMI measurements do not distinguish between fat and fat free mass (FFM) and are therefore unable to determine tissue composition change associated with illness, weight gain, growth or nutritional rehabilitation.[43] Knowledge of body composition is clinically important in CF as depleted or lower fat free mass status may lead to poor lung function.[48]

Currently there is limited data on body composition and clinical outcomes in CF populations. Fat free mass depletion has been shown to be associated with more severe lung disease,[49] impaired respiratory function and loss of diaphragm muscle mass.[50] Hidden FFM depletion (i.e. those with a BMI in the healthy range but low FFM) has been found in adults with CF when body composition has been assessed using dual energy X-ray absorptiometry (DXA) compared to when using BMI alone.[49–51] In addition, high body fat percentage in normal BMI individuals with CF, has been shown to be inversely associated with lung function.[52] Recurrent pulmonary exacerbations have been associated with reduced FFM, bone mineral density and worse lung function particularly in young adult men.[53,54]

Pre-pubertal females have been found to have a deficit in FFM using a four compartment model (DXA, air displacement plethysmography and labelled water dilution).[55] Children with a BMI greater than the 10th percentile have been shown to have FFM depletion associated with reduced lung function and bone mineral loss indicating that malnutrition would have been underestimated if defined by BMIp alone.[36,48] Lean body mass index (LBMI) has been found to be strongly associated with lung function in male children regardless of BMIp, whereas in female children LBMI has been associated with lower lung function in those who have a BMI below the 50th percentile.[48]

Whole body DXA is the most accurate method of body composition measurement available in the clinical setting for CF. Bioelectrical impedance analysis (BIA) and skinfold thickness (SKF) measurements of body composition have been found to be less accurate when assessing FFM in CF when compared to DXA.[48,51] One of the main limitations of BIA and SKF measurements is that assessment methods have not been validated for CF and reference data is derived from healthy non-CF populations.

Whilst knowledge about body composition in CF is clinically important, the lack of availability of low cost equipment validated for the CF population may make it difficult to use outside the research setting. There is increasing interest in the use of handgrip strength, a validated measure of peripheral muscle mass that is simple to use in clinical practice, which has been shown to be correlated to lung function.[56]

Body composition assessment methods are not currently used, in the majority of CF centres, as a routine part of nutritional assessment and monitoring in day-to-day clinical practice.

2.4 Good practice points

2.4.1 Infants and children

- In children aged 2–18 years nutritional advice and interventions should be aimed at maintaining BMI on or above the 50th percentile as this is associated with better lung function.
- Weight should be measured at each clinic visit and hospital admission.
- Height/length should be measured at each clinic visit and hospital admission.
- Head circumference (up to two years of age), should be measured 1–2 weekly until thriving and then at each clinic visit and hospital admission.
- BMI percentile in children aged 2–18 years is the universally accepted measure of nutritional status in CF and should be calculated at each clinic visit and hospital admission.
- All weight, height, head circumference measurements should be plotted on the age-appropriate UK-WHO growth chart.
- No single measure of nutritional status should be used to define malnutrition in infants and children with CF.

2.4.2 Adults

- In adults, nutritional advice and interventions should be aimed at maintaining a BMI of 22kg/m2 in women and 23kg/m2 in men, as these are associated with better lung function.
- Weight should be measured at each clinic visit and at least twice per week throughout hospital admissions.
- Height should be measured at each clinic visit and hospital admission in all people with CF until growth has ceased.
- Maximal attained height should be used for calculation of BMI and lung function.
- BMI is the universally accepted measure of nutritional status in people with CF and should be calculated at each clinic visit and hospital admission.
- Height, weight and BMI should be recorded longitudinally and in a graphical format to assist in the evaluation of changes in nutritional status.

3. Nutritional management

3.1 Introduction

Despite continued improvement in the respiratory and nutritional management of CF, malnutrition, primarily due to an energy deficit, remains a problem for some people.[7,57] It is therefore essential that growth and nutritional status are monitored frequently (see section 2), to allow early identification of malnutrition and prompt treatment.

Energy requirements vary widely between people with CF and in individuals during the course of their life. Factors affecting energy requirements include age, gender, nutritional status, chronic and acute infection, gastro-oesophageal reflux and control of malabsorption (in those who are pancreatic insufficient). In the past, energy requirements were estimated to be approximately 120–150 percent of the Estimated Average Requirement (EAR) for the normal population.[58] Energy needs are now quoted to be 110–200 percent of those required by healthy individuals of the same age and gender.[7] The Scientific Advisory Committee on Nutrition (SACN) dietary reference values[59] should be used as a starting point when estimating energy requirements. As there is a high degree of variability in energy requirements it is important that nutritional needs are assessed on an individual basis taking the factors above into consideration.[60] People with CF who are PS generally have lower energy needs and fewer nutritional problems than those who are PI.

Many studies have indicated that some children and young adults with CF do not meet these recommended energy requirements despite nutritional interventions.[17,19,61,62]

There are currently no guidelines for the optimal daily protein intake required by people with CF therefore research is needed to establish recommendations for optimal protein intakes.[7,63]

3.2 Factors compromising dietary and energy intakes

3.2.1 Appetite

Dietary intakes are often compromised by a poor appetite associated with both chronic and acute respiratory infections. People with CF often identify the start of a chest infection by a sudden and dramatic loss of appetite. Vomiting, excessive coughing and expectoration of a large volume of sputum may all contribute. The loss of appetite tends to follow a pattern, decreasing prior to and during a chest infection and subsequently improving once the infection is treated and there is clinical improvement. Appetite may also be compromised by gastro-intestinal complications e.g. chronic and acute constipation, distal intestinal obstruction syndrome (DIOS) and gastro-oesophageal reflux. There is little work specifically exploring appetite regulation in CF, therefore in practice appetite is difficult to measure and quantify. One of the roles of the Specialist CF Dietitian is to offer advice and counselling to try and improve appetite.

3.2.2 Knowledge

Disease related nutritional knowledge in children with CF and their families has been shown to be poor, with gaps in knowledge and misconceptions about diet being apparent.[64–67] For families to successfully manage a chronic illness a high level of adherence with therapy is required and studies suggest good factual knowledge can contribute to improved adherence.[68,69] In 2010 the UK Cystic Fibrosis Trust carried out a survey to seek the views of carers of children with CF and adults with CF, on the care and services provided to them. This survey highlighted the importance of nutritional knowledge to people with CF and their carers.[70]

3.2.3 Other factors

It is important to consider the impact that the constant emphasis placed on food, eating, weight gain and nutritional status has on adherence.[60] In some, depression, behavioural problems and disordered eating may also result in erratic eating habits leading to a reduced energy intake.

3.3 Dietetic management

All people with CF should have access to a Specialist CF Dietitian at every outpatient clinic visit, inpatient admission and at the time of an annual review.[24,71]

Dietetic management depends on nutritional and clinical status. Advice should be tailored to individual needs, taking age, nutritional and pancreatic status, financial and family circumstance, religious and cultural dietary beliefs and food preferences into account. For most people with CF, nutritional intervention programmes should emphasise a high-energy intake and intensive nutritional management.[72] Increasing the energy content of the normal diet, oral nutritional supplementation, behavioural interventions, enteral tube feeding and parenteral nutrition have all been shown to improve weight gain in people with CF.[73,74] However, recent Cochrane reviews have highlighted a lack of randomised controlled trials examining the effects of nutritional interventions for weight gain in people with CF.[75,76] Therefore nutrition guidelines are largely based on experiential learning, expert opinion and advise a staged approach to nutritional intervention.[39,77]

In the past these nutritional guidelines have used weight, height and weight for height as cut off points for different levels of nutritional support. More recently BMIp position for people with CF aged two to 20 years and BMI values for adults have been recommended as more accurate predictors of nutritional risk.[7] Percentile positions for BMI have also been validated as a part of a nutrition risk screening tool for children and adolescents with cystic fibrosis two–20 years of age.[78] This document recommends that BMIp positions should not be used in isolation to assess nutritional status in growing children (see section 2). In children BMIp position may mask nutritional stunting and genetic short stature. Suggestions for different stages of nutritional management for infants, children, adolescents and adults are given in table 3.

Interventions should be tried stepwise for a limited period of time until nutritional status is optimised.

Table 3: Stages of nutritional management

	<12 months	1–2 years	2–18 years	>18 years
Normal nutritional status Preventative nutritional counselling	Weight, length and head circumference increasing at expected rates for age	Weight and length increasing at expected rates for age	BMIp 25–75th **or** Weight and length increasing at expected rates for age	BMI 20–25kg/m2
Additional nutritional support Further strategies to enhance energy content of diet +/-use ONS	Correction of nutritional deficits present at diagnosis **or** Weight gain less than expected for age over 2–8 weeks **or** Acute disease related reduction in appetite	Weight loss or no weight gain over 6– 8 weeks **or** Acute disease related reduction in appetite	BMIp <25th **or** Weight loss or no weight gain over 4–6 months **or** Acute disease related reduction in appetite	BMI< 20kg/m2 **or** Weight loss over 4–6 months **or** Acute disease related reduction in appetite
Intensive nutritional support Discuss benefits and use of enteral tube feeding	Sustained deviation from previous weight and/or length percentile	Sustained deviation from previous weight and/or length percentile	Persisting BMIp<25th **or** Sustained deviation from previous weight and/or height percentile	Persisting BMI <20kg/m2 **or** Continuing weight loss
Overweight Consider strategies to reduce rate of weight gain or in significant cases weight reduction		Significantly increased weight velocity or weight over 2 percentile positions above height percentile	BMIp >91st	BMI >25 kg/m2

3.3.1 Good practice points

- All people with CF should be seen regularly by a Specialist CF Dietitian.
- Dietitians should assess and address all factors which may compromise appetite and dietary intake.
- Dietetic interventions should be tailored to the individual needs of people with CF.

3.4 Preventative nutritional advice

The aim of preventative advice and support is to achieve normal rates of weight and height gain in infants and children and to maintain or optimise weight and BMI in adults. All people with CF should receive preventative or anticipatory nutritional counselling regardless of their age and clinical or nutritional status.

3.4.1 Feeding infants, toddlers and young children

National newborn screening (NS) for CF has been available in the UK since 2007. Newborn screening allows treatment to commence by approximately four weeks of age and is associated with positive nutritional outcomes.[4,79,80] Early diagnosis gives the opportunity to prevent previously reported nutritional problems, including faltering growth, anaemia, vitamin deficiencies and hypoalbuminaemia.[81]

3.4.2 Infants

Most infants with CF will gain weight and grow normally if fed either breast milk or a normal infant formula.[80,82,83] Breastfeeding should be encouraged as breast milk contains lipase and beneficial nutritional, immunological and growth factors.[39,83] Exclusive breastfeeding has been shown to be associated with improved respiratory outcomes in the first two[80] to three[84] years of life.

For those who cannot breastfeed, or choose not to, standard infant formula will support normal growth in the majority of infants from birth to six months of age. If catch-up growth is required, or malabsorption is difficult to control, energy requirements may be higher (see 3.5.2).

Approximately 15 percent of infants with CF are born with meconium ileus (MI). Although presentation with MI does not ultimately affect nutritional or respiratory status,[85,86] these infants are often nutritionally compromised in early infancy, especially if surgical resection is required.[87] Detailed attention to nutritional management in the acute surgical period often includes the use of parenteral nutrition and hydrolysed protein, medium-chain triglyceride containing feeds (see section 6.1).[88]

Infants derive half of their energy intake from the fat in breast or formula milk and therefore all infants who present with obvious symptoms of malabsorption (pale, frequent and oily stools) should commence pancreatic enzyme replacement therapy on diagnosis of CF (see section 4.3.1).

3.4.3 Sodium supplementation in infants

Infants with CF may require additional sodium supplementation due to high salt losses and the relatively low sodium content of breast and formula milk. Infants particularly at risk include those with high stoma/diarrhoeal outputs, those with pyrexia and those living in hot climatic conditions (see section 5.7.2).

3.4.4 Gastro-oesophageal reflux (GOR) in infants

Gastro-oesophageal reflux is relatively common in infants with CF89 and can compromise growth and exacerbate respiratory symptoms. Treatments include thickening the feed, using a pre-thickened formula, using motility stimulants and reducing gastric acid using H2 receptor antagonists and/or proton pump inhibitors[90,91] (see section 7.11).

3.4.5 Weaning/introduction of solids and feeding toddlers

Weaning foods should be introduced between four to six months of age. This is earlier than current guidelines,92 and helps to achieve optimal protein and energy intake. By the end of the first year a normal to high-fat diet should have been introduced, according to the child's needs. Introducing meat and pulses at an early stage will help to improve the iron and zinc intake in breastfed infants. Due to increased sodium requirements in CF, foods that contain salt should not be restricted e.g. cheese and normal gravy, when weaning (see section 5.7.2). It is also acceptable to use salt in cooking. Full fat cows' milk should replace breast or formula feeds at one year of age. As with the general population monounsaturated and polyunsaturated fat sources should be encouraged in preference to saturated fats. Once an infant is fully weaned sodium supplements may still be required in certain circumstances (see section 5.7.2). As the diet becomes more varied the need for enzyme variation according to fat intake becomes greater (see section 4).

3.4.6 Behavioural intervention

Dietary counselling is essential throughout early childhood when long-term feeding habits are being established. It is important that mealtimes are positive experiences. Unfortunately, food may be used as an effective tool to obtain parental attention and behavioural food refusal may develop.[93–95] Unless carefully handled, this behaviour can persist for a number of years resulting in a poor dietary intake and growth. Attention to the behavioural aspects of feeding, in addition to providing nutrition education has been shown to be more effective

at improving energy intakes and growth than nutrition education alone.[73,96–98] Most nutrition consensus documents now recommend that carers should be routinely provided with written advice to encourage positive eating behaviours.[7,39,83,99] This advice is summarised in table 4. A web-based nutritional management package including both behavioural management strategies and nutrition education has also been developed.[100]

Table 4: Advice to encourage positive eating behaviours

▪ Encourage family meals, so that the child is seated with other children/adults.
▪ Avoid other distractions e.g. having the television on at mealtimes.
▪ 'Good' or 'positive' behaviour should be encouraged by giving lots of attention e.g. "Well done, was that nice?" In this way the child will learn that bad behaviour does not get attention, but good behaviour does.
▪ If the child is slow at eating give gentle encouragement.
▪ Make food as attractive as possible e.g. cutting sandwiches into shapes with pastry cutters
▪ Food play is an important part of learning to feed properly. If the child is “messing” with food – let them, providing that this is not excessive.
▪ Limiting meal times to 30 minutes is a good rule of thumb. Allowing mealtimes to drag on for longer than this rarely results in more food being eaten. After 30 minutes food should be removed without comment
▪ If the child completely refuses to eat and appears to be seeking attention (e.g. screaming, throwing the food), the food should be removed without comment and the child should wait for the next meal/snack time. An alternative should NEVER be offered.
▪ Punishment has more impact if carried out sparingly – e.g. if the child is always being shouted at, it loses impact. The behaviour should be acknowledged but not reinforced/rewarded, by giving attention.
▪ When instructions such as "stop throwing food" are issued, make sure the child carries them out. Otherwise the child will win and the behaviour is reinforced/rewarded.
▪ Likewise if a particular punishment is threatened (e.g. going to bed early) for a particular behaviour and the behaviour occurs, the punishment should always be carried out. This should happen as soon as possible after the behaviour has occurred, so that the child can see the connection with the behaviour and learn.
▪ Empty threats or threats that cannot possibly be carried out (e.g. you won’t come on holiday unless you eat that) should be avoided, otherwise the child will learn that the threat of discipline is meaningless.
▪ It is important to advise all caregivers to be consistent on all of the above points otherwise the child will be living by different sets of rules and will not know what to expect. This confusion will perpetuate bad behaviour.

3.4.7 School age children

As children get older, energy requirements increase. In children with CF, respiratory infections and worsening chest symptoms may further increase requirements. It is important however, that children with CF do not feel any different from their peers when eating. Normal school meals or packed lunches are appropriate for the majority of children. If weight gain and growth are concerns a high-fat snack or supplement to be taken at break times may be requested for the child. By school age most children will manage to swallow their enzyme capsules whole. Young children will however, still need guidance with doses and supervision with administration. As children get older, it is important to encourage independence with taking PERT at school. Children should be encouraged to learn about their PERT and to always carry enzymes with them. Some schools can find self-medication a problem and it may be necessary for the CF Nurse Specialist/Dietitian to discuss the need for independence with this aspect of treatment with the staff. It is important that schools are aware that PERT should be taken at the same time as eating and not given before or after the child goes into the dining hall. Most schools can provide information about the menu. This enables the carers or Specialist CF Dietitian to give advice on correct pancreatic enzyme doses. If packed lunches are taken, a note should be put in the box giving advice on the correct doses for the individual foods the child may eat. As with infants, sodium supplements may still be required in certain circumstances (see section 5.7.2).

3.4.8 Adolescents/adults

Adolescence is a physically and emotionally demanding period associated with increased nutritional requirements due to rapid physical growth and pubertal changes; these factors may adversely impact on nutritional status and lung function.[101] Age and treatment related complications of CF e.g. cystic fibrosis-related diabetes (CFRD) and osteoporosis lead to further challenges in maintaining an optimal nutritional status throughout adulthood.

Adolescence is a phase of developing independence, autonomy and personal identity. Teenagers have a profound desire to be independent and may engage in risk taking behaviours. Food choice is a likely target for testing this independence. Adolescents with chronic conditions are at risk of developing disordered eating.[102] Although formal eating disorders are uncommon in people with CF, disturbed eating is reported.[103] Enteral tube feeding may also impact on eating behaviours and body satisfaction.[104] Increased awareness of eating disturbances in adolescents with CF is required (see section 6.4).[103,104] In addition, treatment adherence may need addressing. Positive and optimistic attitudes have been shown to enhance quality of life and facilitate treatment adherence.[105]

3.4.9 Good practice points

- Regular age specific dietary counselling from an experienced Specialist CF Dietitian is required for all people with CF.
- The majority of infants with CF should be fed breast milk or a standard infant formula.
- Infants presenting with MI may benefit from a hydrolysed protein formula, especially if surgical resection is required.
- Any signs of GOR should be investigated and treated promptly.
- Weaning should commence between four and six months of age.
- Routine advice should be given regarding the behavioural factors that may affect food intake.
- In any age group the need for additional sodium supplementation should be assessed on an individual basis.
- Mealtimes should be relaxed, pleasurable experiences at home and at school.
- Attention should be given to body image and adherence issues in adolescents and adults with CF.

3.5 Moderate nutritional deficit

3.5.1 Improving Growth and Nutritional Status

Frequent monitoring of growth, nutritional status and appetite will enable early recognition and treatment of deficits (see section 2). Before considering any form of nutritional intervention there should be a full review and if possible correction of all factors that could contribute to malnutrition, including a detailed review of PERT (see section 4) and exclusion of CFRD.

3.5.2 Infants

The importance of regular growth assessment in the first few months of life cannot be overemphasised. In infants who are breastfed, where weight gain is poor despite optimal PERT, increasing the frequency of breastfeeding, or giving a complementary formula feed will help to increase the energy intake.[106] For formula fed infants, a nutrient dense infant formula or carefully supervised feed concentration should be considered. Attention should be given to the protein:energy ratio of the feed and therefore the sole addition of fat and/or carbohydrate supplements should be avoided.[107]

Growth failure may be related to, or exacerbated by a poor sodium intake.[83,88,108] If growth failure is a problem sodium status should be checked and if required sodium supplementation given (see section 5.7). Zinc deficiency related to malabsorption is also known to contribute to poor growth in CF.[109] The North American evidence based guidelines recommend that zinc supplementation (1mg elemental zinc/kg/day in divided doses) should be considered in infants with poor growth.[83]

Due to the inaccuracy of plasma/serum zinc levels this recommendation is made without checking zinc status. If there is no response to treatment after six months the supplementation is stopped.

3.5.3 Improving the energy content of the diet – all ages

If weight gain is poor, the first stage to increasing the energy intake is by using foods with high calorie content. The most effective way of doing this is by using high-fat foods, paying attention to increasing unsaturated as well as saturated fats. For some people with CF small frequent meals and snacks rather than being over faced with large portions at mealtimes is more successful in increasing the overall energy intake. The Specialist CF Dietitian should give individualised advice on the most appropriate strategy. In 2010, a survey on the needs of people with CF and carers highlighted the importance of providing practical dietary advice, including menu options and recipes for families.[70]

A recent study has highlighted the over-dependence on saturated fat in the CF diet.[61] This is potentially of concern, as increased life expectancy suggests that the diet should be as cardio-protective as possible. It is therefore prudent to encourage the consumption of mono and poly-unsaturated fats. These fats may also improve serum essential fatty acid status,[110] which may be associated with health benefits, including improved growth.[87,111]

3.5.4 Good practice points

- In infants, if weight gain is poor, energy intake can be improved by increasing the frequency of breastfeeding, introducing complementary formula feeds or using a high-energy infant formula or carefully supervised feed concentration.
- Sodium and zinc supplementation should be considered in infants with suboptimal growth.
- Undernourished infants, children and adults with CF should be encouraged to eat a higher-fat diet.
- Monounsaturated and polyunsaturated fat sources should be encouraged.

3.6 Oral nutritional supplements (ONS)

If nutritional status remains poor despite encouraging a high-energy diet, addressing behavioural factors, ensuring optimal PERT and excluding CFRD, then ONS may be beneficial for some people with CF.[7,83] A Cochrane review of three randomised clinical trials, including a total of 131 patients (mainly children) suggested a lack of evidence of the efficacy of these products to improve nutritional status in children with CF and mild malnutrition. The review concluded that although ONS may be beneficial for some, they should not be regarded as an essential part of CF care.[76]

In practice, prescribed carefully on an individual basis, ONS can be used successfully in undernourished people with CF to improve energy intakes and weight.[19,112–115] Short-term use of ONS may help to avoid a decline in total nutritional intake and hence weight loss associated with illness related anorexia. Supplement use during acute respiratory exacerbations may not increase weight and BMI in all; however it may prevent further weight loss and decline in BMI. Further studies are required to assess the efficacy of ONS in these different circumstances.[74]

The quantity and timing of ONS intake is important as they should provide additional nutrition and should not replace meals. There are a wide variety of ONS available in different presentations and flavours. Age, individual preference and nutritional needs should be taken into consideration when deciding on which to use, as all have different properties and nutritional composition.

3.6.1 Good practice points

- Oral nutritional supplements may be considered in children and adults with CF who have sub-optimal growth rates and nutritional status, despite maximising oral dietary intake and optimising PERT.
- Oral nutritional supplements can help to prevent weight loss during acute respiratory exacerbations.
- Oral nutritional supplements should be taken in addition to an optimised daily food intake.
- The use of ONS should be monitored for tolerance, ongoing need, adherence and improvement in nutritional outcomes.

3.7 Significant nutritional deficit

3.7.1 Enteral tube feeding (ETF)

If nutritional status is deteriorating or failing to improve after routine management and the use of ONS have been optimised, ETF should be considered. This form of nutritional support is an integral part of overall care for many people with CF and requires close clinical evaluation. It is stressed that any intervention should be in keeping with local policies and guidelines.

A Cochrane systematic review did not identify any eligible randomised controlled trials that have assessed the efficacy of ETF in CF.[75] However, in non-randomised studies ETF is widely reported to improve weight gain and nutritional status[74,116–118] and to stabilise or slow the rate of decline in lung function.[117,119] Improved quality of life following gastrostomy placement has also been reported.[120] Early intervention is associated with improved outcomes[116,119,121] and therefore ETF should be introduced to those who it will potentially benefit as an early component of CF care.[83,122,123]

Most studies have shown ETF should be continued long-term, to achieve significant improvement in catch up growth, lung function and positive changes in body composition.[116–119,121]

3.7.2 Route of feeding

Individual preference and clinical status determine the route for ETF. Nasogastric (NG) and gastrostomy feeding are the two most commonly used methods. Naso-jejunal, gastro-jejunal or jejunostomy feeding may be beneficial if clinically indicated e.g. in severe gastroparesis and gastro-oesophageal reflux.

3.7.3 Nasogastric (NG) feeding

Nasogastric feeding (NG) may be the preferred option for some people with CF due to personal preference, or when gastrostomy placement may be unsuitable or high-risk because of the presence of oesophageal or gastric varices or during pregnancy. Discussion regarding the appropriate route of feeding with gastroenterologists or liver specialists is helpful to aid appropriate decision making.

Nasogastric feeding is usually considered a less permanent method of nutritional support. It may be used successfully for short-term support during respiratory exacerbations, as an episodic nutritional boost to maintain growth, or as a trial prior to gastrostomy feeding. Local hospital feeding policies and current NPSA guidelines should be followed when undertaking NG feeding. Success depends on attitude and motivation, with some people with CF preferring to place a NG tubes every night for feeding on a long-term basis because of concerns about body image related to gastrostomy placement.

The main disadvantages of NG feeding are that tubes can be dislodged by coughing, gastro-oesophageal reflux (GOR) may be exacerbated, swallowing enzymes with a tube in situ may be problematic for some, tubes may be unpleasant and difficult to pass (especially for those with nasal polyps) and the tube can have a negative impact on body image.[75]

3.7.4 Gastrostomy feeding

Gastrostomy feeding is the preferred route of ETF for long-term nutritional support. Percutaneous endoscopically placed gastrostomy tubes, radiologically inserted gastrostomy tubes or low profile gastrostomy buttons are used. Local hospital gastrostomy feeding policies should be followed with regard to suitability for tube placement, types of tube used and care of the stoma site and equipment.

Like NG feeding, gastrostomy feeding may be associated with complications including nausea, vomiting, GOR, tube dislodgement or blockage, disturbed sleep, disturbed body image, leakage, granulation and infection around the gastrostomy site and inconvenience with preparing and cleaning feeding equipment. Most complications are mild and transient.[75] If GOR is a problem, medical therapy should be optimised, and in some cases surgery (Nissen's fundoplication) may be indicated.

As with any procedure requiring anaesthesia optimising pulmonary treatment pre- and post-gastrostomy placement is essential. Pain relief to enable good physiotherapy is required for the first few days after gastrostomy insertion.

3.7.5 Feed administration

Feeds are usually administered as continuous overnight infusions, as bolus feeds (gravity or pump assisted) during the day or a combination of both. The advantage of nocturnal feeds is that high-energy diets can be continued throughout the day.

3.7.6 Types of feed

A wide variety of enteral feeds are available. The feed chosen, the method and rate of administration should be appropriate to age, nutritional requirements, clinical condition, preference and lifestyle. The majority of people with CF tolerate a high-energy (1.5 to 2.4 Kcal/ml) polymeric feed (with or without fibre),however an elemental, semi-elemental or medium chain triglyceride (MCT) containing feed may be beneficial if a polymeric feed is not tolerated.

3.7.7 Pancreatic enzyme replacement therapy and enteral tube feeds

Both polymeric and elemental feeds require PERT. The dose and timing of administration of pancreatic enzymes should be determined on an individual basis, taking the type, fat content and rate of infusion of feed into consideration. If the feed is infused over a long period of time only small enzyme doses may be required.[124] This may be partly due to the stimulation of gastric lipase activity[125] and due to the slow infusion of fat. Pancreatic enzymes are usually given orally at the beginning and end of overnight feeds. Bolus feeds may need a higher dose of enzymes as larger volumes and hence more fat, are given over shorter periods of time. Where possible, enteric coated enzyme preparations should be given by mouth and should not be put down NG or gastrostomy tubes as they may block the tube. Section 4.8 gives advice for on how to manage people with CF, receiving ETF, who are unable to swallow pancreatic enzymes.

3.7.8 Monitoring

Following the introduction of ETF, weight, height and BMI should be monitored closely. The amount of feed given should be adjusted according to the rate of weight gain. The objective of feeding is that weight gain should result from an increase in lean body tissue and so weight gain should not be too rapid. Feed tolerance should also be monitored. If reflux, vomiting or malabsorption are noted the rate of feeding or PERT may need adjusting.

It is also important to monitor glucose tolerance at the time of introduction of ETF. Blood glucose should be checked mid and immediately post-feeding. Recommendations suggest this should be repeated on a monthly basis at home.[20,126] Many centres in the UK choose to repeat measurements on an individual basis taking into account clinical and nutritional status. In cases of nocturnal hyperglycaemia a small dose of insulin may be required to cover the feed.

3.7.9 Good practice points

- Enteral tube feeding should be considered if age appropriate rates of growth or nutritional status are not maintained despite attention to energy and nutrient intake from food, oral supplements and optimum PERT.
- The choice of route and timing of feed administration should be determined on an individual basis.
- Polymeric feeds with or without fibre should be used for the majority of people with CF.
- Semi-elemental, elemental and MCT containing feeds may be beneficial in those who do not tolerate polymeric feeds.
- Pancreatic enzymes should be given orally with enteral tube feeds.
- Glucose tolerance should be monitored at the time of introduction of ETF and repeated according to clinical and nutritional status.

3.8 Appetite stimulants

Appetite stimulants may play a role in treating malnutrition in a minority of people with CF when reduced energy intake is secondary to poor appetite. They should only be used when all other causes of malnutrition have been ruled out and more conventional nutritional support strategies have been unsuccessful or declined.[127] The evidence of efficacy and safety of drugs to stimulate the appetite is limited. Therefore before they are used, the risk/benefit must be discussed within the multidisciplinary team and with the patient and carers. Evidence from larger clinical trials is required before they are used routinely.[128]

Megesterol acetate a progesterone derivative with a side effect of weight gain is the most studied appetite stimulant in CF. Short-term use of megesterol acetate has been found to improve body fat, lean body mass, weight and respiratory function in CF.[129] However, it is associated with undesirable side effects, including reversible adrenal suppression, insomnia, mood changes and irreversible impaired glucose intolerance and diabetes.[129–131]

Cyproheptadine hydrochloride is an antihistamine which is known to stimulate the appetite. Two studies have reported improvements in weight and height in children and adults with CF.[132,133] Cyproheptadine hydrochloride was reported to be safe to use with minimal side effects.[132,133]

Other drugs such as dronabinal, olanzapine and mirtazipine have been used in other conditions to stimulate appetite, but they are not routinely used as appetite stimulants in CF. Mirtazapine is an antidepressant used in adults with CF; positive side effects some people experience are appetite stimulation and weight gain.

3.9 Anabolic agents

A limited number of studies have looked at the use of anabolic agents in people with CF. Treatment with insulin like growth factor 1 has been studied, but evidence of value is poor.[134] Recombinant human growth hormone (rhGH) has also been studied and has been shown to improve weight gain, lean body mass and growth in people with CF.[135–138] However rhGH treatment is invasive and expensive. Side effects include mild oedema, arthralgia, carpal tunnel syndrome, gynecomastia, insulin resistance and glucose intolerance.[135–137] A recent multicentre trial reported improvements in growth and lung volumes in CF, however further studies are required to establish safety and effectiveness,[139] before rhGH is used in routine clinical practice.[138,139]

Treatment of impaired glucose tolerance with early insulin therapy shows more promise. A decline in nutritional status and lung function in the years preceding the diagnosis of CFRD was reported in an early study[140] though is not inevitable in all.[141] A number of studies have reported improvements in nutritional status following early treatment with low dose long acting insulin.[142–145]

3.10 Parenteral nutrition (PN)

Parenteral nutrition is not routinely recommended as a method of long-term nutritional support for people with CF. This form of nutritional support is usually reserved for those with a non-functioning gut e.g. as a consequence of gastrointestinal surgery or prolonged bowel obstruction. Most commonly PN is required following intestinal resection in infants presenting with MI (See section 6.1).[106]

3.11 Good practice points

- Ensure all other causes/reasons for malnutrition or weight loss have been excluded before considering treatment with appetite stimulants or anabolic agents.
- The benefits and side effects of appetite stimulants/anabolic agents must be discussed with the patient and consent must be obtained prior to use.
- Early insulin therapy can be considered in those with impaired glucose tolerance.
- Parenteral nutritional support should be reserved for those with a non-functioning gut.
- With all treatments there must be very close monitoring and documentation of clinical parameters and side effects throughout treatment.

4.0 Pancreatic enzyme replacement therapy

4.1 Introduction

Pancreatic dysfunction occurs in the majority of people with CF.[146] Pancreatic enzyme replacement therapy (PERT) has a very important role in maintaining adequate nutritional status. Untreated pancreatic insufficiency will result in maldigestion and malabsorption of intestinal fat and to a lesser extent protein, consequently contributing to sub-optimal nutritional status and deficiency of fat soluble vitamins.

In routine clinical practice the aims of PERT are to:

- Promote growth, development and the maintenance of normal nutritional status.
- Control the signs and symptoms of malabsorption particularly loose and/or frequent fatty stools, abdominal pain, abdominal cramps, wind and bloating.
- Aim to achieve normal bowel habit and stool characteristics.
- Enable attainment of a high-energy intake by allowing a high-fat diet to be consumed.
- Achieve sufficient fat soluble vitamin and essential fatty acid status.

There are two key components of PERT:

- 1) Efficacy – ensuring that doses are sufficient to achieve optimal absorption of fat and other nutrients. This involves individualised advice on PERT dosing and attention to adjuncts to PERT. Other gastrointestinal factors such as pH and intestinal transit time can impact on digestion of nutrients
- 2) Safety – ensuring that doses comply with the advice of regulatory bodies to minimise the risk of side-effects.[147]

4.2 Determination of pancreatic status

Pancreatic insufficiency and sufficiency are clinical terms describing pancreatic function. Fat digestion is not clearly impaired until lipase output decreases to below 10 percent of the normal level.[148] Pancreatic sufficiency means that there is sufficient residual exocrine pancreatic function to allow normal fat absorption and so PERT is not required.

There is a strong relationship between CF genotype and pancreatic status. People with class I–III CF mutations on both chromosomes are likely to be pancreatic insufficient (PI) whilst those with at least one class IV–V CF mutation are likely to be pancreatic sufficient (PS).[149] However it should be noted that atypical cases have been described including those who are homozygous for class I–III CF mutations and yet appear to be PS. The relationship between genetics and pancreatic status is documented [150] but this does not replace the need for a more objective assessment of pancreatic status.

In the majority of cases an objective assessment of pancreatic status is needed, before starting PERT, to confirm pancreatic insufficiency, as the presence of clinical signs and symptoms suggestive of maldigestion and malabsorption does not accurately determine pancreatic function. Tests to assess pancreatic function include; the co-efficient of fat absorption (CFA), faecal pancreatic elastase 1(FPE-1) serum trypsinogen, 13C mixed-triglyceride breath test and direct pancreatic stimulation studies.[151–154] Some of these investigations are not routinely available in clinical practice.

Of the currently available tests monoclonal faecal pancreatic elastase 1(FPE-1) has been found to be highly predictive of pancreatic insufficiency.[153] It has a high degree of sensitivity and specificity.[155] The test is widely available, relatively easy to perform and is not affected by exogenous PERT so can be used to confirm pancreatic insufficiency in people with CF who have already commenced PERT. In general FPE-1 levels of < 100µg/g stool have been found to be predictive of severe pancreatic insufficiency and the need for PERT. FPE-1 levels of 100–200 µg/g stool are associated with moderate pancreatic insufficiency and the need for PERT in such situations needs to be considered taking into account nutritional status and abdominal symptoms. Caution is needed when interpreting FPE-1 in large volume dilute stool and in premature infants.

Fat malabsorption can be objectively measured and assessed by use of the CFA. In healthy subjects CFA is approximately 90%.[156] The objective of PERT is to achieve a CFA as near to normal as possible thereby contributing to attainment of an optimal nutritional status. To measure CFA stools are collected for 72 hours and a detailed food intake diary is completed. The stools are then analysed for their fat composition. Diaries are used to assess dietary fat intake and the CFA is calculated. However this test is rarely used as many CF Centres in the UK no-longer provide analysis of CFA. Unfortunately in day to day clinical practice there are no tests to enable the objective assessment of the adequacy of PERT.

4.3 Recommendations for commencing PERT

4.3.1 Infants

In infants presenting through newborn screening programmes PERT can be commenced in advance of the FPE-1 result particularly in those with two CFTR mutations associated with pancreatic insufficiency and where there are obvious clinical signs of maldigestion and malabsorption including sub-optimal weight gain at presentation.[83,88] In infants with at least one class IV–V mutation PERT should not be commenced until assessment of FPE-1 is carried out.

Meconium ileus (MI) is usually associated with pancreatic insufficiency. Infants presenting with MI and subsequently diagnosed with CF should have FPE-1 measured to confirm pancreatic status but should be commenced on PERT as soon as oral or enteral tube feeding is established.

4.3.2 Older children and adults

Older children and adults who are diagnosed with CF should have their FPE-1 level checked prior to commencing PERT unless there are obvious signs and symptoms of maldigestion and malabsorption.

4.4 Pancreatic sufficiency

It is important to remember that pancreatic dysfunction evolves over time and even in those who are PS, regular assessment of pancreatic status is indicated.[157] Young people with CF who are PS should have FPE-1 checked annually during infancy and childhood and during periods of weight loss, gastrointestinal disturbances or nutritional decline.[27] There are currently no guidelines on how often FPE-1 should be checked in PS adolescents or adults; as a minimum FPE-1 should be checked if there are new signs and symptoms suggestive of maldigestion and malabsorption or any nutritional decline. PERT should be commenced if the results are indicative of pancreatic insufficiency.

4.5 Selection of type of PERT

Detailed composition of PERT available in the UK can be found on the BNF website.[158] Of the available preparations enteric-coated micro-sphere preparations are recommended. The pH-sensitive coating protects the enzymes from inactivation by stomach acid, dissolving only when the pH exceeds 5.5 within the small bowel, thereby minimising the possible effect of gastric pH on inactivation of PERT. Pancreatic enzyme replacement therapy is available in a range of strengths and presentations.

To minimise signs and symptoms of maldigestion and malabsorption it is important that PERT dosing is adjusted according to the quantity and composition of the food being eaten. Therefore products at the lower end of the enzyme concentration range (5000–10,000 units lipase per scoop or capsule) are preferred for infants and younger children whilst higher strength preparations (22,000–40,000 units lipase per capsule) may be helpful for older children and adults to reduce the number of capsules required.

4.6 Dosage recommendations to optimise efficacy of PERT

A recent Cochrane review showed there is limited evidence on the relative dosages of enzymes needed for people with different levels of severity of pancreatic insufficiency, optimum time to start treatment and variations based on differences in meals and meal sizes.[159] However as the majority of lipase is produced by the pancreas whereas amylase and protease are secreted at other sites in the gastrointestinal tract, dietary fat therefore is particularly dependent on PERT for adequate digestion. Furthermore small cohort studies have demonstrated enhanced CFA when PERT is more closely titrated to fat intake.[160] Clinical and dosing data from cohort studies and audit of clinical practice indicate a similar lipase to dietary fat ratio to achieve the level of fat absorption consistent with a good nutritional status.[161–163] Such studies would suggest doses of 500–4000 units of lipase per gram of dietary fat with a mean requirement of 1800 units of lipase/g dietary fat/day to achieve optimal absorption of fat and other nutrients in children and adults. For infants there is more variability in the dose (see section 4.7.1). Recent advances in enzyme dosing have been described.[106]A full nutritional assessment is required and should include the following:

In the clinical management of CF, healthcare professionals should also consider that:

- Enzyme doses should be determined on an individual basis and take into account dietary fat intake, abdominal symptoms and growth/weight gain.
- Enzyme doses are best reviewed by a Specialist CF Dietitian who can accurately assess food and fat intake and advise on dosing accordingly.
- People with CF and their families require advice that is practically related to food intake and not strictly based on units of lipase/g dietary fat.
- Enzyme dosing is only one component of achieving optimum digestion and adjunctive therapies such as proton pump inhibitors and H2 antagonists may be required (see section 4.7.3).
- Other gastrointestinal disorders e.g. Coeliac disease, inflammatory bowel disease, irritable bowel syndrome, food allergies or intolerances can occur or may be already present e.g. short bowel syndrome. If enzyme dosing and adjunctive therapies are thought to be optimal and symptoms of maldigestion, malabsorption or sub–optimal nutritional status remain, other causes should be explored.

4.6.1 Dosage recommendations to ensure safety of PERT

Evidence of complications of PERT are fortunately rare, however in the 1990s a number of serious cases of fibrosing colonopathy (FC), a condition characterised by strictures of the large bowel, were reported.[164] As a result of a subsequent case control study[165] the Committee on Safety of Medicines (CSM) issued the following safety recommendations.[166]

- The total dose of pancreatic enzyme supplements used in people with CF should not usually exceed 10,000 units of lipase per kg body weight daily.
- If a person with CF on any pancreatin preparation develops new abdominal symptoms (or there is any change in existing abdominal symptoms) they should be reviewed by their medical team to exclude the possibility of colonic damage.
- High-strength pancreatin Pancrease HL® and Nutrizym 22® should not be used in children under 15 years of age with CF due to their association with the development of FC.
- No association with FC was found with Creon® 25,000 and Creon® 40,000.
- It is important to ensure adequate hydration at all times in children receiving higher-strength pancreatin preparations.

The occurrence of FC/colonic strictures is very rare in the UK.[1] Cases of FC were seen in the USA between 1995 and 1999 suggesting dose rather than preparation as a contributory factor.[167] Therefore safety of pancreatic enzymes, which are subject to variation of dose by people with CF and their families still requires serious consideration and regular evaluation.

Some people with CF require higher doses than the CSM recommendation of <10,000 units of lipase/kg/day in order to achieve good bowel habit and optimum nutritional status. As this safety dose is a weight based recommendation, doses higher than 10,000 units lipase/kg/day can occur in infants as they consume a higher percentage of energy from fat (50%) and a greater number of calories and hence fat per kg body weight per day than older children and adults. It can also occur in people with a high-energy intake, a high-fat diet, a large appetite or on ETF. In these cases close monitoring is required. Dietary fat should not be restricted in an attempt to maintain the enzyme dose at the safety limit as this may impact on energy intake and the ultimate goal of promotion of good weight gain and growth.

In the UK there is a limited range of PERT available for use. Detailed information on products available can be found in the BNF.[158]

4.7 Practical administration of PERT

As Creon® is the enzyme replacement preparation currently used by 95 percent of people with CF and pancreatic insufficiency in the UK[1] it has been used as a reference in the following practical guidance. This should not be interpreted as a recommendation of one product by the authors and a limited range of alternative preparations are available.[158]

4.7.1 Infants

- Creon® Micro is the most practical pancreatic enzyme supplement for infants. Alternatively enzyme granules from a standard strength capsule can be used.
- The enzyme microspheres should be given orally with feeds. The prescribed dose should be mixed with a little fruit puree or a little of the infants usual milk and given from a baby spoon. Check that microspheres do not remain in the mouth post-feed.
- Timing of PERT administration may be a factor in achieving optimal digestion and absorption so for large volume or longer feeds it is suggested that the total dose is split and given at the start and during the feed.
- The starting dose should be based on the presenting clinical picture taking into account weight since birth, bowel symptoms and feed volumes.

Table 5: Suggested starting doses for PERT in infants with CF

Breast fedinfants	Standard infant formula	Nutrient dense infant formula
¼–½ scoop Creon® Micro 'short breastfeed' (<20 minutes) ½–1 scoop Creon® Micro 'long breastfeed' (>20 minutes)	¼–1 scoop Creon® Micro per 50–100 ml	½–1 scoop Creon® Micro per 100ml

- Increase the dose gradually by ¼–½ scoop of Creon® Micro at each feed until bowel symptoms are controlled, weight gain optimised whilst being mindful of the safety guidance.
- For infants who have undergone surgery for MI see Section 6.1.

4.7.2 Children and adults

Children and adults diagnosed with pancreatic insufficiency should start with:

- 1–3 capsules standard strength enzymes (Creon® 10,000) per meal or snack

Enzyme capsules should be swallowed whole at as early an age as possible and most children can manage this from the age of four to five years. The microspheres should not be crushed or chewed as this will reduce enzyme effectiveness. For young children or those who are unable or unwilling to swallow whole capsules:

- The enzyme microspheres may be mixed with a small quantity of food and given immediately. Microspheres should not be mixed with the whole meal
- The microspheres may be taken directly from opened capsules with a drink

4.7.3 Efficacy of PERT

The evidence on the effect of timing of enzyme dosing on digestion and absorption is limited but it may influence the efficacy of PERT. If taken before the meal or with fluids the microspheres may be emptied from the stomach before they have mixed with food.[168,169] If taken after the meal food may leave the stomach before enzymes.[169] Splitting of enzyme doses at main meals with ½–$^2/_3$ of the total dose required given at the beginning of the meal and ½–$^1/_3$ given during the meal may enhance efficacy and allow the dose to be titrated to the amount eaten and fat content of the meal. This may be a helpful strategy but given the evidence base should not be employed if it impacts on the enjoyment of eating. Dividing doses during the course of the meal can be helpful in avoiding taking too many enzymes if the meal is not completed.

People with CF who have a poor response to PERT or high dosage requirements may benefit from changing the timing of PERT administration.[168] Consideration should also be given to the use of adjunctive therapies such as proton pump inhibitors and H2 antagonist to reduce gastric acid secretion and facilitate optimal PERT efficacy.

Continual education regarding PERT is important and should take into account changes in clinical, physical and psychological status.[170]

4.7.4 Practical advice

The following practical advice will help people with CF:

▪ Enzymes should be taken with all food and drinks that contain fat
▪ Enzymes are not needed with foods or drinks that do not contain fat such as squash, fizzy drinks, fruit juice, fruit or boiled/jelly sweets
▪ Enzyme doses should be titrated according to dietary fat intake. Certain very low fat foods containing high amounts of protein e.g. protein shakes, low fat yogurts, lean meat may require PERT
▪ Enzyme doses should be individualised and people with CF taught to adjust doses depending upon the quantity and content of food consumed and on their gastrointestinal symptoms and nutritional status
▪ Enzyme requirements will vary considerably between individuals
▪ People with CF who have a poor response to PERT or high dosage requirements may benefit from changing the timing of PERT administration
▪ Enzyme preparations should be changed to suit needs for example progress to standard strength preparations when a young child is able to swallow capsules; move on to higher strength preparations when enzyme capsule number is inconvenient. When changing to higher strength preparations it is very important to maintain a similar lipase dose
▪ Enzyme doses should not be increased if adherence is poor
▪ Adequate hydration is important when taking enzymes

4.8 Administration of PERT via feeding tubes

People with CF who are intubated and ventilated will be unable to swallow PERT capsules. Some clinicians may continue PERT regardless whether they are feeding or not to assist with the digestion of mucus in the GI tract. There is no evidence base to guide this practice.

To maximise the digestion and absorption of enteral tube feeds the administration of a low dose of PERT via the feeding tube should be considered. This can be in the form of a powdered enzyme preparation which has been dissolved in water or enteric coated enzymes which have been dissolved in sodium bicarbonate.171 In very young infants this practice has the potential risk of excess bicarbonate which needs careful clinical assessment. A proton pump inhibitor will be required as the enzyme activity of the dissolved enzymes will be destroyed in the acidic stomach environment.

4.9 Atypical presentations

Occasionally atypical presentations may arise, for example individuals who are homozygous for genetic mutations known to be associated with pancreatic insufficiency but who thrive and appear to be asymptomatic; those with transient levels of FPE-1; people who are PS but who appear to gain symptomatic relief from the use of pancreatic enzymes. In these situations lower doses of PERT than generally recommended may provide symptomatic relief and each case needs to be assessed individually in discussion with the multidisciplinary team to decide on optimum symptom control, nutritional management and dose.

4.10 Good practice points

- Pancreatic enzyme replacement therapy is key to supporting good nutritional status for the majority of people with C.F
- Enteric coated microsphere preparations are recommend for people with CF.
- The evidence on dosing for efficacy is limited but food and fat based dosing may enhance the co-efficient of fat absorption thereby minimising the impact of maldigestion on nutritional outcome.
- Pancreatic enzyme dosing and efficacy should be reviewed regularly by a Specialist CF Dietitian.
- Clinicians and people with CF should always be made aware of the complexity of bowel function in CF and that enzyme dosing advice is a guideline and not an exact pharmacological science.

5.0 Vitamins and minerals

5.1 Introduction

Malabsorption of fat soluble vitamins is likely in most people with CF, particularly those who are PI. Biochemical evidence of fat soluble vitamin deficiency occurs early in infants diagnosed with CF by newborn screening.[172–175] A significant correlation between vitamin A and E deficiency and pancreatic insufficiency has been reported at the time of diagnosis but no correlation is reported between pancreatic status and vitamin D deficiency.[175]

Factors that may contribute to fat soluble vitamin deficiencies in CF include:[176]

- Fat maldigestion and malabsorption as a consequence of pancreatic insufficiency and bile salt deficiency.
- Fat maldigestion and malabsorption due to suboptimal PERT or poor adherence to PERT especially with vitamin replacement therapy.
- Poor dietary intake due to anorexia or poor dietary sources of vitamins.
- Poor adherence to prescribed fat soluble vitamin supplementation.
- Inappropriate vitamin supplementation regimens.
- Increased utilisation and reduced bioavailability.
- Short gut syndrome due to previous bowel resection.
- CF-related liver disease.
- Chronic antibiotic use.

Newborn screening allows earlier intervention with PERT and the early introduction of appropriate fat soluble vitamin supplementation. With advances in our understanding of fat soluble vitamin metabolism vitamin status needs to be considered in the context of modern disease where there is an overall improvement in nutritional status, improved life expectancy and new and emerging co-morbidities.[177] Traditionally, vitamin status was considered in terms of overt deficiency resulting in the classically recognised deficiency symptoms. Vitamin status may now be considered in the context of subclinical deficiencies or health outcomes rather than overt deficiency.[177] It is increasingly recognised that sub-clinical deficiencies in CF may be of importance.

All people with CF should have plasma fat soluble vitamin levels checked annually.[39,83] In paediatric care these tests are often performed in the non-fasting state as it is difficult to fast an infant. Some of the investigations should be done in the fasting state e.g. zinc and parathyroid hormone and it is suggested that in adults these tests together with assessment of vitamins A, D and E can be combined and done in the fasting state. Most people with CF who are PI will require supplementation with the fat soluble vitamins A, D, E and K. In people who are PI vitamins should be taken with food and PERT. Most people with CF who are PS require supplementation with vitamin D and some may require additional vitamin A, vitamin E and/or vitamin K.

Educating people with CF about the roles of vitamins may help improve adherence to vitamin supplementation.[178]

5.2 Vitamin A

Vitamin A (retinol or retinol esters) can be absorbed from the diet or synthesised from the dietary precursor's alpha and beta carotene. Many vitamin supplements contain both retinol and its pro-vitamin carotene forms. Vitamin A is absorbed in the small intestine and circulates in the serum as a complex of retinol and retinol binding protein (RBP) and is stored in the liver as retinyl esters. Serum retinol levels reflect vitamin A status only when liver stores are severely depleted or excessively high. Therefore liver stores can be high despite normal or low serum levels however liver biopsy is not a feasible monitoring process. Low serum levels of vitamin A have been shown to be unrelated to the degree of fat malabsorption in CF.[179] Serum retinol levels should be used as a guide as in clinical practice they are the only readily accessible test available.

5.2.1 Signs and symptoms of deficiency

Vitamin A is a fat soluble vitamin that plays a role in the eye (dark adaptation), skin, respiratory and immune systems. Vitamin A deficiency may cause night blindness and can proceed to xerophthalmia in CF.[180] There are multiple case reports of night blindness in CF with the earliest in 1968.[180] Cohort reviews have confirmed both conjunctival xerosis and night vision problems in CF.[181] Facial nerve palsy has also been reported.[182,183] Symptoms improve when low serum levels of vitamin A are corrected with supplementation. Observational cohort studies have suggested an association between low vitamin A levels and low lung function.[184] Cross-sectional data suggest that in young people with CF, FEV_1 correlates positively with serum retinol levels regardless of age, pancreatic function or nutritional status.[185] Though this finding is not repeated in all studies.[186]

5.2.2 Toxicity

Despite only one case report of vitamin A toxicity in a newly diagnosed infant with CF[187] there is currently concern about the potential for toxicity of vitamin A.[177] There are reports of higher levels of vitamin A in people with CF following lung transplantation.[188,189] Acute toxicity can cause vomiting, abdominal pain, anorexia, blurred vision, headaches and irritability and chronic toxicity can cause headache, muscle and bone pain, ataxia, skin disorders, alopecia, liver toxicity and dyslipidaemia. Other recognised complications of hypervitaminosis A such as benign intracranial hypertension are very rare.

Retinol is teratogenic and caution with supplementation is advised during pregnancy. Current Department of Health recommendations for the non-CF population are that pregnant women or women who may become pregnant should be advised not to take supplements containing vitamin A and should not eat foods rich in vitamin A such as liver and liver based products.[190]

Ideally, in women with CF serum levels of vitamin A should be checked in the preconceptional period. If levels are normal it would appear prudent to continue Vitamin A supplements at a dose of less than 10,000 IU of retinol/day (the maximum recommended daily supplement of vitamin A at any time during pregnancy).[191] Women should be individually assessed and the final decision regarding the level of supplementation should take into account plasma vitamin A levels, the availability of vitamin A rich foods in the diet (especially if oral nutritional supplements or enteral tube feeds are being incorporated) and whether supplementation can be advised.[192]

5.2.3 Monitoring

Blood retinol levels may be low due to low levels of retinol binding protein (RBP). Retinol binding protein is produced in the liver and is an acute phase reactant.[193–195] Circulating RBP levels may therefore be low and plasma vitamin A levels may be falsely depressed in people with liver disease or during acute infection or inflammation. Secondary vitamin A deficiency may also occur as a consequence of zinc deficiency as zinc is required for production of RBP.

Vitamin A samples need to be processed quickly and protected from light to avoid degradation. If vitamin A levels are low samples should be checked for light degradation and RBP, plasma zinc and a marker of infection e.g. C reactive protein should be measured before increasing supplementation to accurately interpret results.

5.2.4 Supplementation

People who are PI with evidence of low plasma levels should take daily vitamin A supplements with food and pancreatic enzymes. Current recommendations advise starting with low doses of vitamin A, using retinol as the preferred source. Doses should be increased according to serum levels which should be checked three–six monthly after dose changes.[196] Current recommendations for starting doses are summarised in Table 6.

Table 6: Recommendations for starting doses of vitamin A

Age	Daily dose
Infants	<1500IU (0.45mg)
>1 year	1500–10,000IU (0.45–3.0mg)

5.2.5 Good practice points

- People with CF who are PI and show evidence of low plasma levels should take daily vitamin A supplements with food and pancreatic enzymes. Doses should be adjusted depending on plasma levels.
- People with CF who are PS should only be commenced on vitamin A supplementation if plasma vitamin A levels are low at a time of clinical stability.
- In pregnancy, serum retinol levels should be measured ideally preconceptionally or early in the pregnancy and dose adjusted according to levels.
- Following transplantation vitamin A levels should be monitored annually; reduction or discontinuation of vitamin A supplementation should occur if levels exceed the reference range.

5.3 Vitamin D

There are two nutritionally significant compounds with vitamin D activity: ergocalciferol (vitamin D2) and colecalciferol (vitamin D3). Dietary sources of vitamin D do not make a major contribution to vitamin D status. A significant contribution to vitamin D status occurs by exposure of 7-dehydrocholesterol present in skin to sunlight or ultraviolet light irradiation which causes the production of vitamin D3 (colecalciferol). Due to the latitudinal position of the UK vitamin D production from sunlight occurs usually only between April and October.[197,198]

5.3.1 Signs and symptoms of deficiency

Severe vitamin D deficiency causes rickets in children and osteomalacia in adults. In CF, suboptimal vitamin D status may be one of the many factors that contribute to the aetiology of low bone mineral density and increase the risk of low trauma fracture.[199,200] Low levels of 1,25 dihydroxy vitamin D (1, 25(OH)2D) increase the production of PTH, resulting in increased bone turnover and bone loss, particularly in cortical bone.

People with CF have a high prevalence of vitamin D deficiency and numerous studies have reported low levels of 25-hydroxy vitamin D (25OHD) in their clinic populations despite supplementation.[201–204]

Vitamin D deficiency in CF may be due to a number of factors:[205]

- Reduced absorption of dietary and supplemental vitamin D due to pancreatic insufficiency.
- Low BMI leading to reduced capacity for vitamin D storage in adipose tissue.
- Reduced levels of vitamin D binding protein.
- Impaired hepatic hydroxylation of vitamin D.
- Reduced sunlight exposure due to poor health or photosensitivity with quinolone antibiotics.

Vitamin D status has also been positively associated with improved lung function in CF.[201,203,206,207] There is increasing interest in its role in other aspects of lung disease through its action on regulating inflammation, inducing antimicrobial peptides, and/or its action on muscle.[201,203,206–208] The precise relationship between vitamin D status and lung health remains unclear.

5.3.2 Monitoring

Serum 25OHD levels are the most reliable measure of vitamin D status. The assay used to measure 25-hydroxyvitamin D should measure both vitamin D2 and vitamin D3 and be totalled as this is essential to accurately determine vitamin D status. There is limited evidence for or against having fasting levels of serum 25-hydroxyvitamin D measured. However seasonal variation should be taken into consideration when assessing vitamin D status.

There is currently no consensus on optimal vitamin D levels for bone health in the CF population. Guidelines vary from 50nmol/l (20ng/ml)[200,209] to 75nmol/l (30ng/ml).[210,211] The recommendation for healthy paediatric population is 50nmol/l[212] and the healthy adult population is 75nmol/l (30ng/ml).[213]

Achieving an adequate vitamin D status can be difficult in people with CF.[201,214] There is evidence that vitamin D3 (colecalciferol) may be more effective than vitamin D2 (ergocalciferol) at increasing and sustaining serum vitamin D levels. Vitamin D2 is more rapidly catabolised and its effect may be more transient.[206,215,216]

Current recommendations for vitamin D supplementation in CF are broad at 400–2000IU daily for infants and 400–5000IU daily for children over one year and adults.[200,211] Vitamin D3 (colecalciferol) is preferable to D2 (ergocalciferol) due to its efficacy. Supplementation should be individualised dependent on serum levels. Any change in supplemental dose should be monitored with repeat serum measurements three to six months after dose adjustments, taking into account adherence to supplements and seasonal variation.[217]

There are some people with CF whose requirements are above these recommendations and will only achieve sufficient levels with higher daily doses of vitamin D especially during the winter months. All supplementation should be individualised and based on regular monitoring and assessment of adherence.

Ultraviolet radiation and UVB light therapy have been shown to be as effective as vitamin D2 in improving serum levels in people with CF but adherence to this type of therapy can be poor and it may be an unrealistic therapeutic option for many to include in heavy treatment regimens.[218,219]

Table 7: Recommendations for starting doses of vitamin D

Age	Vitamin D, per day
Infants	400–2000IU (10–50µg)
>1 year	400–5000IU (10–125µg)

5.3.3 Good practice points

The assessment of vitamin D status should include serum 25-hydroxyvitamin D, serum calcium and parathyroid hormone concentrations

- Assessment of response to changes in supplemental dose should be undertaken by measuring vitamin D levels three months to six months after the change.
- People with CF who are PI should take daily vitamin D supplements with food and pancreatic enzymes.
- People with CF who are PS should be commenced on vitamin D supplementation depending on plasma levels or in line with guidelines for the UK population.

5.4 Vitamin E

There are several forms of Vitamin E, but the major physiological form is alpha tocopherol.

5.4.1 Signs and symptoms of deficiency in CF

Vitamin E acts as an antioxidant reducing the effects of free radicals produced by infection and chronic inflammation, thus helping to protect cell membranes from oxidative damage. Studies have shown that many newly diagnosed people with CF have low vitamin E levels, irrespective of pancreatic function.[220] Vitamin E deficiency has been associated with haemolytic anaemia in infants[221] and may cause ataxia, neuromuscular degeneration[222] and compromised cognitive function.[223] Oxidative stress is enhanced in CF due to chronic respiratory inflammation.[224] Studies suggest that people with CF have inadequate antioxidant defences to cope with elevated oxidative stress.[224] Therefore, vitamin E may be important in controlling the progression of lung disease.

5.4.2 Toxicity

High plasma vitamin E levels have been reported in people with CF who are PI.[225] Hypervitaminosis E only occurs with very large supplemental doses and may cause bruising and bleeding with increased prothrombin time. This is due to inhibition of vitamin K dependent carboxylase and can be reversed by administering vitamin K. Other symptoms may include fatigue, weakness and gastrointestinal upset. This emphasises the need for regular nutritional assessment and surveillance.

5.4.3 Monitoring and supplementation

Routine monitoring of vitamin E levels is recommended annually. Serum or plasma concentrations represent only a small proportion of total body vitamin E, which is largely found in cell membranes. Serum levels are usually measured in clinical practice to assess vitamin E. Serum levels will vary according to levels of the carrier lipoproteins; to overcome this vitamin E concentrations can be expressed in relation to serum lipid levels, which requires a fasting blood sample. In people with CF with abnormal lipid levels it may be beneficial to consider vitamin E in relation to lipid levels. In CF a minimum cut off ratio for alpha-tocopherol:cholesterol ratio of 5.4mg/g has been suggested.[225]

Routine supplementation should be started in all people with CF who are PI at diagnosis and in people who are PS if low plasma vitamin E levels are detected. The water soluble vitamin E supplements have no advantage over fat soluble versions, as long as the supplement is taken with pancreatic enzyme preparations.[226]

Recommended doses vary internationally.[39,83,227] This variability is due to a lack of strong evidence on optimal doses, earlier intervention and the improving clinical condition of people with CF.

Table 8: Recommendations for starting doses of vitamin E

Age	Vitamin E (IU), per day
0–12 months	40–80
1–3 years	50–150
4–7 years	150–300
8–18 years	150– 500
Adults	150– 500

Conversion to milligrams is dependent on the type of vitamin E in oral supplements. DL-Alpha-tocopherol: from IU to mg multiply by 0.9 and D-Alpha-tocopherol from IU to mg multiply by 0.67.

Doses should be adjusted in response to serum levels.

5.4.4 Good practice points

- People with CF who are PI should take daily vitamin E supplements with pancreatic enzymes and food.
- Levels should be measured annually and status assessed.
- In people with CF who have abnormal lipid levels it may be beneficial to consider vitamin E in relation to lipid levels.

5.5 Vitamin K

Vitamin K exists naturally in multiple dietary forms. It is not a single compound but a group of homologous fat-soluble compounds. Absorption of vitamin K from the gut depends on bile salts and pancreatic lipase secretion stimulated by dietary fat. Risk factors for vitamin K deficiency in CF include fat maldigestion and malabsorption, bile salt deficiency, liver disease, chronic antibiotic use, bowel resection and inadequate dietary intake.[228]

5.5.1 Signs and symptoms of deficiency

Vitamin K is important for blood coagulation and bone health. It is an essential cofactor in the post-translational conversion of glutamyl (Glu) to y carboxyglutamyl (Gla) residues. Undercarboxylated Gla-dependent proteins are functionally inactive. Major Gla-proteins (active) include prothrombin, osteocalcin and other bone metabolism-related proteins. More recently interest has been shown in vitamin K's role in energy metabolism and inflammation[229] which may be of importance in CF.

Although rare, coagulopathies including haematomas, intracerebral haemorrhage and severe life threatening bleeding in people with CF and vitamin K deficiency continue to be reported.[230–232]

Studies suggest subclinical vitamin K deficiency is common in CF.[233,234] Persistent subclinical vitamin K deficiency despite supplementation with varying doses of vitamin K has also been reported suggesting the appropriate dose of vitamin K has yet to be established.[235–238] However, in a study of children and adolescents with CF supplementing with 1-5mg vitamin K1 /day for one month there was an improvement in vitamin K status but the majority of patients remained in the suboptimal range.[239]

Increased levels of undercarboxylated osteocalcin have been reported in CF and have been associated with reduced lumbar spine bone mineral content,240 reduced levels of bone markers for bone mineral accrual[204,234,240] and increased levels of markers for bone turnover.[234]

5.5.2 Monitoring

In clinical practice most CF specialist centres do not assess vitamin K status routinely.[241,242] Plasma levels of vitamin K are an unreliable measure of status.[77] Prothrombin time reflects only vitamin K deficiency of the liver and is an insensitive marker of vitamin K status. The presence of circulating Gla-proteins in their undercarboxylated forms is the most sensitive indicator of vitamin K deficiency but it appears that different vitamin K dependant proteins have different vitamin K requirements. Protein or prothrombin induced by vitamin K absence or antagonism (PIVKA II) is a more sensitive indicator of vitamin K deficiency of the liver. Undercarboxylated osteocalcin is the most sensitive indicator of vitamin K status of the bone and is the first Gla-protein to occur in the undercarboxylated form in deficient states.[243]

5.5.3 Supplementation

Vitamin K1 (phytomenadione) is preferred over menadione salts as it is deemed the safest form of supplementation.[196] Routine supplementation with vitamin K1 is now recommended for all people with CF who are PI.[196,200,210,211,244]

Table 9: Recommendations for starting doses of vitamin K[211]

Age	Vitamin K
Babies and infants <2 years	300µg/kg/day rounded to the nearest mg
Children 2–7 years	5mg/day
From 7 years	5–10mg/day

5.5.4 Good practice points

- Routine supplementation with vitamin K1 (phytomenadione) in people with CF and pancreatic insufficiency is recommended

5.6 Water-soluble vitamins

Water-soluble vitamins appear to be well absorbed. Significant deficiencies of water-soluble vitamins are rarely reported in CF. Routine supplementation of water-soluble vitamins is unnecessary unless there is documented evidence of poor dietary intake or biochemical deficiency. Parenteral vitamin B12 may be required for people with CF who have had extensive surgery for meconium ileus or distal intestinal obstruction syndrome.[39,245]

Currently the role of antioxidant vitamins is under investigation.[246] Antioxidants may help to protect against oxidative lung damage caused by infection. Low levels of vitamin C[247] and impaired status of glutathione and carotenoids[248,249] have been reported in CF. The Cochrane review examining antioxidant supplementation for lung disease in CF concluded that there appeared to be conflicting evidence regarding the clinical effectiveness of antioxidant supplementation. Further trials are required to determine the need for and effects of antioxidant supplementation.[250]

5.7 Sodium

People with CF are susceptible to sodium depletion as a result of increased sodium loss in sweat with exercise or in hot environmental conditions. Infants are particularly susceptible due to low dietary intakes from breast milk or standard infant formula (approximately 1.6mmol/kg body weight for every 200ml/kg fed) and high body surface area relative to weight. High-energy formula and protein hydrolysate formula have a higher sodium content and therefore the variable sodium content should be taken into consideration. Sodium status is further compromised if the infant is pyrexial or has excessive losses through diarrhoea or stoma output following surgery for neonatal gastrointestinal complications.[88,106] Sodium depletion is characterised by hyponatraemia, decreased appetite, nausea, vomiting, lethargy, headaches, muscle cramps, and inadequate weight gain in infants.[58] Hyponatraemia can also contribute to thicker sputum which is more difficult to expectorate[108] and may contribute to distal intestinal obstruction syndrome.[251]

5.7.1 Monitoring

Sodium deficiency in CF is difficult to determine. Whilst fractional excretion of sodium in relation to creatinine (FENa) is an appropriate marker of sodium depletion[196] it requires paired blood and urine samples. Urinary sodium:creatinine ratio (UNa:Cr) has been shown in one study in CF to correlate with FENa and is a less invasive marker of sodium depletion.[252] In routine clinical practice UNa:Cr should be used to assess sodium status and sodium supplementation considered if this is abnormal. However urinary sodium is often used as an approximate estimation of sodium status as it is easier to measure. Low urinary sodium has been shown to be associated with poor growth in non CF infants following intestinal surgery.[253–255] Two of these studies have suggested that sodium supplementation should be considered if urinary sodium levels are less than 30mmol/l.[253,255]

5.7.2 Supplementation

In Europe, using a modified Delphi process, consensus could not be agreed for recommending routine sodium supplementation in all infants.[88] In infants, the need for sodium supplementation should be assessed on an individual basis, taking climate and sodium losses into consideration. In most cases supplementation with 1–2mmol/kg should correct deficiency,[88] although more may be required in hot climatic conditions or for high diarrhoeal or stoma losses.[106] Routine sodium supplementation may be recommended for some older children, adolescents or adults.

Additional sodium may be required in the following groups:

- Infants, especially during hot weather, illness and in those with stomas.
- In children in hot weather or when dietary intakes are poor.
- In all people with CF during hot weather (especially during foreign travel) or before strenuous exercise.
- In all people with CF during illness when there may be increased losses due to pyrexia and reduced intake due to decreased appetite.
- In any situation that may causes excessive sweating or losses e.g. occupational hazards, motor-biking in warm weather.

Sodium supplements may be given to infants in the form of sodium chloride solution added to expressed breast milk, infant formula or infant fruit juice drinks, and to diluted fruit squash for toddlers or as oral rehydration supplements (e.g. Dioralyte® or Electrolade®). Sodium supplements are usually given as salt tablets for older children and adults.

With increasing age all people with CF should be encouraged to eat a diet high in sodium, including the use of salt in cooking, added to food at the table and high salt foods. Sodium supplemented sports drinks may also be useful. Advice should be given to increase fluid intake for people with CF receiving sodium supplements.

Table 10: Recommendations for sodium supplementation based on current practice in the UK

Age	Sodium supplementation
Up to 1 year	1–2mmol/kg body weight or up to 500mg
Children over 1 year	Up to 4g in divided doses
Adolescents and adults	Up to 6g in divided doses

5.7.3 Good practice points

- Urinary sodium:creatinine ratio or urinary sodium should be routinely checked in all breast and formula fed infants.
- Infants with low urinary sodium:creatinine ratio or urinary sodium should be given additional sodium supplementation with sodium chloride solution to initially provide an additional 1–2mmol/Kg/day. Urinary sodium should be checked and additional supplements given as necessary.
- The dose should also be adjusted as weight increases.
- In infants in hot ambient temperatures or with increased water loss due to pyrexia, diarrhoea, increased stoma output, tachypnoea or increased sweating sodium requirements may be higher.
- Consideration should be given to additional sodium supplementation in older children, adolescents and adults in hot ambient temperatures, during intense exercise or with increased water loss due to pyrexia, diarrhoea, increased stoma output, tachypnoea or increased sweating.

5.8 Calcium

Calcium balance can be disrupted in CF due to malabsorption and increased faecal losses,[256] inadequate dietary intake and glucocorticoid therapy.[256] In addition gastric acid increases the solubility of calcium salts and the use of proton pump inhibitors may contribute to reduced absorption of calcium.

Calcium deficiency results in demineralisation of the skeleton leading to osteopenia. Severe calcium deficiency in CF is rare. Low bone mineral density (BMD) is a common complication of CF. A high calcium intake is associated with reduced fracture risk in the general population[257] and is a positive predictor of bone mineral status in adolescents with CF.[258] Calcium supplementation in children and adults with CF has been shown to have beneficial effects on BMD.[259–261]

Whilst studies report good mean calcium intakes in people with CF[262,263] due to the potential for negative calcium balance, consumption of a high calcium diet should be advised particularly during adolescence. In girls with CF bone calcium deposition has been shown to be greatest during early puberty[264] and related to net calcium absorption.

5.8.1 Recommendations

Table 11: Recommendations for calcium intake[200]

Age	Calcium intake per day
0–6 months	210mg
7–12 months	270mg
1–3 years	500mg
4–8 years	800mg
9–18 years	1300mg
19–50 years	1000mg
>50 years	1200mg

Those with suboptimal calcium intakes should be advised to increase dietary sources of calcium. Calcium supplements should be prescribed if dietary intake is below the recommended intake. Before commencing bisphosphonate therapy for low bone mineral density calcium intake and vitamin D status must be optimised.

5.8.2 Assessment of status

Serum calcium levels are an inadequate measure of dietary calcium adequacy.

If serum calcium levels are outside the normal range, pathological rather than nutritional causes should be suspected e.g. hypo/hyperparathyroidism, chronic renal failure or malignancy.

5.8.3 Guidance on high intakes

People with CF who have a high intake of milk and dairy products in addition to enteral feeds or supplements may exceed the safe upper limit for calcium intake if prescribed calcium supplements. For the general population this is 1500mg of supplemental calcium.[265] Whilst calcium requirements for CF are higher than the general population very high intakes of calcium should be monitored. There is an increased risk of renal calculi in CF but evidence that a high calcium intake is associated with this is inconclusive.[266]

5.8.4 Good practice points

- Encourage a high dietary intake of calcium for all age groups but particularly adolescents.
- Calcium supplementation should be prescribed for those who do not achieve the recommendations.

5.9 Magnesium

Serum magnesium concentrations are a poor indicator of total active ionised magnesium levels.

In CF hypomagnesaemia appears to be mainly related to nephrotoxic effects and proximal renal tubular damage associated with the use of frequent and prolonged courses of high dose aminoglycoside antibiotics.

Other risk factors for magnesium deficiency in CF include:

- Treatment with N-acetylcysteine and diatrizoate sodium powder; a water-soluble contrast agent (HYPAQUE or gastrografin).[267]
- Cystic fibrosis-related diabetes.[268]
- Proton pump inhibitor use.[269]

Hypomagnesaemia is usually asymptomatic but severe symptomatic magnesium deficiency has been reported.[270–272] Hypomagnesaemia was reported in 57 percent of people with CF referred for lung transplantation[273] possibly due to long-term intravenous antibiotic use. The annual monitoring of serum magnesium levels is recommended.[274]

5.9.1 Magnesium supplementation

Most NHS hospital trusts will have their own clinical guidelines for the management of hypomagnesaemia and local protocols should be followed.

5.9.2 Good practice points

- Serum magnesium levels should be measured annually.
- All people with CF receiving courses of aminoglycosides should have regular monitoring of their serum magnesium levels.
- Awareness that people with CFRD or those on long on prolonged courses of PPIs may be at increased risk of magnesium deficiency.

5.10 Zinc

5.10.1 Signs and symptoms of deficiency

Zinc deficiency results in growth retardation, delayed secondary sexual maturation, poor appetite, diminished taste acuity, impaired immune function, mental lethargy and dermatitis. It can also contribute to secondary vitamin A deficiency due to depression of RBP synthesis in zinc deficiency.[275] Conversely, vitamin A deficiency may reduce absorption and lymphatic transport of zinc by altering the synthesis of zinc dependant binding proteins.

5.10.2 Monitoring

Plasma or serum zinc is the most widely used assessment method although their sensitivity and specificity are poor. Albumin is the main carrier protein for zinc and serum levels may decrease during the acute phase response to infection. Levels should be tested in the fasting state as there are diurnal variations and levels fluctuate after meals.

Serum levels are usually low in severe deficiency, but often normal in people with marginal deficiency. The most reliable method for diagnosing marginal zinc deficiency is a positive response to zinc supplementation e.g. improved growth (see section 3.5.2) or an improvement in vitamin A status (see section 5.2.3).

5.10.3 Supplementation

For infants with CF under two years of age who are not adequately growing despite adequate energy and PERT, the North American CF Foundation recommends a trial of zinc supplementation (1mg elemental zinc/kg/day in divided doses for six months).83 These doses are lower than the requirements to correct deficiency (see Table 12).

Table 12: Recommendations of zinc supplementation for correction of deficiency

Age	Zinc sulfate monohydrate: 125mg (45mg zinc) tablets (Solvazinc®)
Child under 10kg	½ tablet daily
Child 10–30kgs	½ tablet 1–3 times daily
Adult and child>30kgs	1 tablet 1–3 times daily after food

5.10.4 Good practice points

- Zinc levels should be tested in the fasting state.
- The most reliable method for diagnosing marginal zinc deficiency is a positive response to zinc supplementation e.g. improved growth.
- A trial of zinc supplementation for infants with CF under two years of age who are not adequately growing despite adequate energy and PERT should be considered.

5.11 Iron

Iron deficiency is common in people with CF and has been reported as occurring in 12% of people under 16 years of age and increasing to 58% of those over 40 years of age.[276] There are numerous factors that contribute to iron deficiency in CF including malabsorption, chronic infection and inflammation, inadequate intake, liver and renal disease, medications such as PPIs and blood loss in haemoptysis, GI losses or menorrhagia.

People with CF who have plasma iron deficiency tend to have iron deficiency anaemia (IDA), poorer lung function[276,277] and more severe disease.[277,278]

5.11.1 Assessment of status

Assessing iron status via laboratory results in CF is complicated by chronic inflammation. Ferritin, an iron storage protein, indicates body iron reserves and is usually low in IDA. However ferritin is also an acute phase reactant and is elevated in acute and chronic infection and inflammation. It may be important to distinguish between iron deficiency anaemia, anaemia of chronic disease (ACD) and a mixed anaemia.

Table 13: Serum levels that differentiate anaemia of chronic disease from iron deficiency anaemia[279]

Variable	ACD	IDA	ACD AND IDA
Iron	Reduced	Reduced	Reduced
Transferrin	Reduced to normal	Increased	Reduced
Transferrin saturation	Reduced	Reduced	Reduced
Ferritin	Normal to increased	Reduced	Reduced to normal
Soluble transferrin receptor	Normal	Increased	Normal to increased
Ratio of soluble transferrin receptor to log ferritin	Low (<1)	High (>2)	High (>2)
Cytokine level	Increased	Normal	Increased

5.11.2 Supplementation

Appropriate advice on ensuring the adequacy of dietary iron intake should be given to all people with CF.

There have been concerns about supplementing with iron as many bacteria require iron for replication and respiration and iron can increase the virulence of bacteria. Studies have suggested that increased airway iron in CF may play a role in facilitating Pseudomonas aeruginosa infection and may contribute to anaerobic biofilm growth.[280,281]

A recent randomised, double-blind, placebo-controlled crossover trial of low dose ferrous sulphate (325mg daily for six weeks) showed supplementation increased serum iron and transferrin saturation from base line without correcting anaemia (haemoglobin) after six weeks. There was no significant effect on sputum iron, pulmonary exacerbation score or sputum microbiome.[282]

5.11.3 Good practice points

- Appropriate advice on ensuring the adequacy of dietary iron intake should be given.
- The use of iron supplementation should be assessed on an individual basis.

5.12 Antioxidants

Antioxidants are a fundamental part of the body's defence system. There is an antioxidant/oxidant imbalance in CF.[224,283] This is accounted for by an increase in oxidative stress, especially in the lungs with increased inflammation with neutrophil activation against invading bacteria and a decrease in antioxidant defences caused by poor absorption of the fat-soluble antioxidants.

5.12.1 Supplementation

There appears to be conflicting evidence regarding the clinical effectiveness of antioxidant supplementation in CF. Further studies are necessary before a firm conclusion regarding effects of antioxidant supplementation can be drawn. An optimal dose and timing of antioxidant supplementation has yet to be determined.[250]

5.12.2 Good practice points

- Further studies are necessary before a firm conclusion regarding effects of antioxidant supplementation can be drawn.
- The optimal dose and timing of antioxidant supplementation has yet to be determined.

5.13 Essential fatty acids

The essential fatty acids (EFA), linoleic acid (omega -6) and alpha linolenic acid (omega -3) are essential components of cell membranes, and are involved in hormone synthesis and immune function. The EFA status of people with CF is variable, and in general status is better in people with CF who are PS.[284] Dietary fat malabsorption contributes and a defect in fatty acid metabolism caused by the CFTR mutation may also be important.[285]

Clinical signs of deficiency are rare, although suboptimal levels may increase susceptibility to respiratory infections with *S. aureus* and *P. aeruginosa*.[286]

Routine supplementation is not recommended, as the most effective dose is unknown and an imbalance of EFA may be harmful.[287]

5.13.1 Good practice points

- Routine supplementation with EFA is not recommended, as the most effective dose is unknown and an imbalance of EFA may be harmful.

5.14 Probiotics

Several small supplementation studies have shown a reduction in intestinal inflammation[288–291]and improvement in clinical and biochemical markers of intestinal function.[290–292] The long-term administration of probiotics may also decrease the incidence of pulmonary exacerbations in CF.[291,293–295] However, the effects of probiotics in CF appear to be temporary.[295] Further research is needed before routine supplementation is recommended to establish the ideal probiotic strain, dosage and impact on health.

There have been case reports of Saccharomyces boulardii fungemia in people with CF who have permanent venous access devices (portacaths/ PAS ports) who were taking Saccharomyces boulardii therapy, so care should be taken in immuno-compromised patients and in those with portacaths/PAS ports/lines insitu.[296]

Antibiotics can cause disturbance in gastrointestinal flora which may lead to reduced resistance to pathogens such as Clostridium difficile. There is increasing evidence of a high carriage rate of Clostridium difficile in people with CF[297,298] and this is particularly problematic in people post-transplant.[299] There is moderate-quality evidence to suggest that probiotic prophylaxis in the non-CF population are safe and effective for preventing Clostridium difficile-associated diarrhoea.[300]

5.14.1 Good practice points

- Further research is needed before routine probiotic supplementation is recommended.

6.0 Nutritional challenges

6.1 Care of infants presenting with meconium ileus (MI)

Up to 20 percent of newborns with CF present with MI.[301] The condition is caused by an intestinal obstruction due to inspissated meconium in the small bowel and often results in the development of a micro colon. Meconium ileus can be found in association with other small bowel complications such as volvulus, intussusception, atresias and meconium peritonitis secondary to perforation. In some infants MI may be detected antenatally by the presence of echogenic or dilated bowel loops on the ultrasound scan. Management varies according to the severity of the obstruction. In mild cases MI may be managed conservatively using oral/nasogastric mucolytics and/or contrast enemas to clear the obstruction. However, many infants require surgical removal of the inspissated meconium. The surgery may involve simple removal of the meconium from the small bowel or in more severe cases, intestinal resection may be required. Following surgery a primary anastomosis may be possible but many will require the formation of a temporary ileostomy.

Some studies report that infants who present with MI, particularly those who have undergone surgical resection, are at increased risk of nutritional deficits later in life, especially if premature or of a low birth weight.[301] However, there are also studies that report no long-term differences in nutritional[85,86,302] or respiratory[86,302,303] outcomes between infants presenting with MI and those who present symptomatically later in life.

Infants who require surgery often present considerable challenges in the management of feeding and PERT.[106] It is important that these infants are managed at a specialist centre for CF care and neonatal surgery.

In the post-operative period following stoma formation parenteral nutrition (PN) is often required until oral or enteral tube feeding can be fully established and weight gain can be maintained. Parenteral nutrition is known to be associated with a number of complications such as cholestasis, therefore appropriate selection of parenteral lipids[304] and early introduction of oral feeding is required to minimise these risks.

If the infant has received conservative management, breast milk or standard infant formula is recommended. Following surgical intervention the choice of enteral tube feed is determined by stoma position, the extent of small bowel resection and parental preference for breast or formula milk. Breastfeeding or giving expressed breast milk has multiple benefits and should be encouraged as the first choice of feed following surgery.

If breast milk is not available, hydrolysed protein and low osmolality medium-chain triglyceride containing feeds should be used.[82]

Infants with MI may have nutritional deficit; those who are breastfed may require complimentary feeds and bottle-fed infants will require feed volumes of 180-200ml/kg to achieve optimum weight gain and growth. If this is not achievable then the use of more concentrated hydrolysed protein formula or nutrient dense infant formula may be indicated but this should be introduced slowly with careful monitoring of GI tolerance and with appropriate pancreatic enzyme supplementation.

Meconium ileus is associated with pancreatic insufficiency so all infants presenting with MI will require PERT when feeds are introduced, irrespective of the feed used. A confirmatory faecal pancreatic elastase 1 should be obtained (see section 4.2). Consideration should also be given to sodium supplementation. Infants presenting with MI, particularly those with stomas are at increased risk of sodium deficiency which can be associated with poor growth (see section 5.7).

6.1.1 Good practice points

- Infants with CF who have undergone surgery for MI should be managed at a specialist centre for CF care and neonatal surgery with input from a Specialist CF Dietitian.
- Infants who have had conservative management of MI the feeds of choice are ideally breast milk or if this is not available standard infant formula.
- Infants who have had small bowel resection and/or stoma formation the feeds of choice are ideally breast milk or if this not available a hydrolysed protein formula.
- If PN is required in the early post-operative period this should be weaned slowly to ensure optimum weight gain and growth whilst establishing full oral feeding.
- For all infants following MI where nutritional deficit is present specific attention must be paid to appropriate feed volume and choice of feed to achieve catch up weight gain.
- The need for additional sodium should be assessed on an individual basis.

6.2 End-stage nutritional support

Maintaining or improving nutritional status in those with deteriorating lung function is challenging. As lung function declines energy requirements are increased secondary to worsening infection, inflammation and increased work of breathing. Frequent respiratory exacerbations are associated with increased sputum production which can cause nausea, vomiting and reduced dietary intakes. The frequency and duration of hospital admissions may also increase with some people with CF spending long periods of time in hospital. Regular dietetic input during this time is paramount.

As lung function declines breathlessness becomes a major problem. Breathing patterns alter in order to reduce respiratory muscle load and this can raise carbon dioxide (CO2) levels. Some people with end-stage CF may require non-invasive ventilation (NIV), often initially overnight to reduce CO2 retention and improve alveolar ventilation.

The ability to eat whilst on NIV will depend on the type of NIV mask used. Full face masks cover the mouth and nose and therefore eating and drinking is difficult. Nasal masks cover the nose only so some people find that they can eat and drink whilst on this mask. Non-invasive ventilation mouth pieces can also be used to facilitate eating and drinking. However with both these options the person needs to be alert enough to synchronise breathing, chewing and eating.

Often people with end-stage CF will require supplementary enteral tube feeding in order to meet their nutritional requirements; this is more common in those on the transplant waiting list. If supplementary enteral tube feeding is necessary it should be instigated before the individual is too unwell to undergo the procedure. The aim of nutritional support in people with end-stage CF is to balance achieving or maintaining optimal nutritional status with quality of life.

People with CF who feed via a gastrostomy can find tolerating feeds more difficult especially if they feed overnight whilst on their NIV. Symptoms will vary according to the duration of time they are on NIV and also the pressure settings on the NIV machine. Abdominal distension, bloating and wind are frequently experienced. In practice the use of prokinetic agents may be of some assistance, and modifying the timing, rate and duration of feed may be helpful. Some gastrostomy tubes can be used for gastric venting (removal of air).

Nasogastric tube feeding and NIV can be more challenging and its use will depend on the type of mask used as a good seal needs to be achieved between the NIV mask and skin for adequate ventilation. Due to locally agreed policies and procedures some hospitals will not initiate NG feeding in people receiving NIV, particularly if this is to be continued in the community. This is due to associated risks of aspiration and tube displacement.

In centres that do NG feed people with CF receiving NIV the problems experienced are the same as those who receive gastrostomy feeds.

Some people with end-stage CF may be sedated and ventilated on intensive care units. In order to meet nutritional requirements these people will require supplementary enteral tube feeding via a NG tube or if present a gastrostomy tube. All supplementary enteral tube feeds require PERT (dosing should be determined on an individual basis (see section 4.8).

6.2.1 Good practice points

- People with end-stage CF face many challenges and regular dietetic input is therefore vital.
- Achieving and maintaining optimal nutritional status needs to be balanced with quality of life.
- People with end-stage CF may require supplementary enteral tube feeding in order to meet their nutritional requirements; this should be instigated before the individual becomes too sick to undergo the procedure.
- All supplementary enteral tube feeds require PERT.

6.3 Overweight and obesity

Preventing nutritional failure is one of the primary concerns in the dietetic management of CF. However with improvements in survival and nutritional status overweight and obesity are becoming an increasingly common problem.[12,13] In the UK during 2014 17 percent of people with CF over 16 years of age were reported to be overweight (BMI 25–29.9kg/m2) and 4 percent were obese (BMI >30kg/m2).1 Older people with CF who are PS are at higher risk of obesity,[305] however it is an emerging problem in paediatric populations and in people with pancreatic insufficiency.[13] Overweight and obesity can also be a particular problem post-transplantation.

There is a positive association between BMI and lung function,[7] however the benefits of increasing BMI on lung function have recently been shown to be diminished above a BMI of 25kg/m2.[305]

Nutritional advice should be individualised to meet changes in nutritional requirements and dietary modifications may be required to support long-term health and well-being. People with CF who are becoming overweight or obese should be given appropriate healthy eating advice in order to lose weight, or prevent further weight gain. In overweight children with CF it is important to ensure height velocity is maintained. With improvements in survival further research into the effects of overweight and obesity in CF is needed.

6.3.1 Good practice points

- Nutritional advice should be individualised to meet changes in nutritional requirements and nutritional status.
- People with CF who are becoming overweight or obese should be given appropriate healthy eating advice in order to lose weight or prevent further weight gain.

6.4 Body image and disordered eating behaviour

Eating disorders are psychological conditions characterised by a persistent, disturbance in a person's eating attitude and behaviour. They are complex and often of multifactorial aetiology. Some studies using non-CF specific tools have suggested that people with CF are at increased risk of developing atypical eating disorders, which have been named eating disorders not otherwise specified (EDNOS).[103] However studies looking at the prevalence of eating disorders in CF show they do not differ significantly from prevalence in the general population.[22,306,307] If an eating disorder is suspected prompt referral should be made to the appropriate specialist team skilled in the treatment of eating disorders.

A tool to measure eating attitudes and behaviours in CF has recently been devised.[308] Disturbed eating attitudes and behaviours in CF include; food avoidance, preoccupation with food, body image disorders and manipulation of PERT.[103] To ensure health and clinical status is not affected the management of people with CF who have disordered eating behaviour and attitudes requires a multidisciplinary team approach which includes a specialist clinical psychologists.

Body image is important to adults, adolescents and children with CF.[22,309,310] Poor body image is related to low self-esteem, depression, anxiety and can influence self- management, adherence and motivation.[310] Differences in satisfaction with body image have been shown between males and females with CF. Females with CF are more satisfied with their body image than males with CF and their non-CF peers despite low weight and BMI.[22,311] In contrast, males appear to want a more muscular body. As low weight is associated with increased morbidity and mortality in CF the association of body satisfaction in women with a low BMI may present a health risk. People with CF who receive enteral tube feeds have also been shown to be less satisfied with their body, have lower self-esteem and a poorer quality of life.[23]

Even though the relationship between CF and the prevalence of eating disorders remains unclear, assessment of people with CF should consider attitudes and behaviours which may impact on nutritional status.

6.4.1 Good practice points

- Management of people with CF who have disordered eating behaviour and attitudes requires a multidisciplinary team approach which includes a specialist clinical psychologist.
- If an eating disorder is suspected prompt referral should be made to the appropriate specialist team skilled in the treatment of eating disorders.

6.5 Nutrition and pregnancy

The nutritional management of pregnancy can be divided into three phases: preconception, pregnancy and post-natal care. There is very little evidence about the nutritional needs for pregnancy in women with CF. Nutritional recommendations are therefore usually based on the requirements established for women without CF and adapted according to our understanding of the additional nutritional requirements for CF.[312,313] Requirements should be individually based taking into consideration preconception nutritional and clinical status. Detailed guidelines for the management of pregnancy in women with CF have been published.[312]

Positive outcomes for both the women with CF and her infant have been associated with better nutritional and clinical status.[312,314,315] As nutritional status plays an integral role in the preconception period and throughout pregnancy a comprehensive nutritional assessment at a Specialist CF Centre by the Specialist CF Dietitian should be carried out ideally in the preconception period. This provides the opportunity to optimise the nutritional status of the woman and to provide appropriate advice. If the pregnancy is unplanned, nutritional assessment and counseling is required as soon as possible. Nutritional assessment and counselling should include:

- Assessment of weight, height, body mass index (BMI), weight history and advice regarding expected weight gain.
- Folic acid supplements (see 6.5.1).
- Assessment of dietary intake and counseling to address the requirements of pregnancy combined with CF.
- Optimisation of nutritional status through staged nutritional intervention including information on the possible need for dietary supplements and/or enteral tube feeding.
- Review of PERT, gastrointestinal symptoms and absorption.
- Assessment of diabetic status by oral glucose tolerance test (in non-diabetics).
- Optimising glycaemic control with conversion to insulin for those on oral hypoglycaemic agents and referral to the Specialist Diabetic/Obstetric Team.
- Measurement of fasting plasma vitamins A, D and E and review of vitamin therapy (including non-prescription items)

6.5.1 Special considerations

Folic acid

It is recommended that all women who are planning a pregnancy take a daily supplement of 400mcg of folic acid in the preconception period and throughout the first trimester.[316,317] Women who have previously had a child with a neural tube defect (NTD) or who are considered to be at high risk of foetal abnormalities e.g. people with diabetes are recommended to take a supplement of 5mg/day.[317]

Vitamin A

Care should be taken to avoid excessive intakes of vitamin A because of the risk of teratogenicity. In practice, supplemental vitamin A is usually continued at a dose of less than 10,000IU retinol/day and plasma levels are closely monitored (See section 5.2).[312]

Weight gain

Though it is unusual to be weighed in the routine antenatal clinic, for women with CF constant surveillance of the woman's nutritional status and weight gain is essential. Nutritional supplementation including enteral tube feeding may be required to achieve adequate weight gain. For normal weight gain in pregnancy an extra 200 kcal/day is needed in the last trimester. Women with CF who have poor nutrition and a low BMI prior to conception will need an increased energy intake during pregnancy.

Gestational diabetes and CFRD

Pre-existing diabetes or gestational diabetes places the women and her baby at an increased risk. Early identification and optimal control of diabetes is essential.[312,318] It is recommended that women with CF without CFRD are screened for glucose intolerance in the preconception period using the oral glucose tolerance test (OGTT).[20,319] It is usual to repeat the OGTT during the first trimester and between 24 and 28 weeks gestation[20,319] or if random blood glucose levels are elevated.[312,318] Blood glucose levels should be measured at every visit and especially during infective exacerbations.

Breast feeding/lactation

Successful breastfeeding in mothers with CF has been achieved.[321] Breastfeeding increases maternal nutritional requirements. Breastfeeding should be discussed with the CF mother throughout pregnancy so that she is aware of the nutritional demands of this. Plans for breastfeeding should be discussed with the CF team to allow for decisions to be made regarding appropriate use of suitable medications post-natally. Individual advice about infant feeding according to the mother's clinical condition and circumstances should be given. Many drugs pass into breast milk resulting in the contraindication of certain medications during pregnancy and lactation or a contraindication to breastfeeding.[312]

6.5.2 Good practice points

- Where possible women with CF should receive preconception nutritional counselling and have a detailed nutritional assessment.
- Supplementation with 400mcg of folic acid or 5mg for those with diabetes/high risk in the preconception period and throughout the first trimester.
- Review of glycaemic status and optimisation of diabetic control ensuring close liaison between CF Centre staff and the obstetric team to ensure effective communication and consistency of management.
- Nutritional supplementation including enteral tube feeding may be necessary to optimise weight gain.
- Usual fat soluble vitamin supplements should be continued during pregnancy and levels monitored but ideally vitamin A should be at a dose of <10,000IU.
- Breastfeeding should be discussed with the mother with CF throughout pregnancy so she is aware of the increased nutritional demand and to help the CF team choose appropriate medications post-partum.

6.6 Lung Transplantation

Lung transplantation is a treatment option for some people with end-stage CF Frequent intravenous antibiotic courses, hospital admissions, early satiety, poor appetite, increased shortness of breath, NIV, nausea, gastrointestinal disturbances and CFRD are some of the challenges faced. At this stage meeting nutritional requirements and preventing weight loss can be difficult. Therefore optimising nutritional status as a fundamental part of routine CF care cannot be over emphasised.

6.6.1 Pre-transplant

Poor nutritional status has been shown to compromise post-transplant survival[322–325] and is a risk factor for post-transplant complications.[326,327] Pre-transplant undernutrition has been shown to be associated with a higher rate of death in lung transplant recipients.[324] However a recent study has shown no difference in post-transplant survival in people with CF with a low BMI (<18.5kg/m2) compared to those with BMI >18.5kg/m2.[328] Most adult transplant centres aim to optimise nutritional status pre-transplant with the aim of achieving a BMI >18kg/m2.[329] A BMI >30kg/m2 is considered a relative contraindication to lung transplantation.[330] Although rare some children with end-stage CF may be referred for transplantation optimising their nutritional status is equally as important.

A detailed nutritional assessment should be conducted at the time of transplant assessment. This should include reviewing PERT, CFRD control, use of oral nutritional supplements/enteral tube feeding and bone mineral density. People with end-stage CF are at an increased nutritional risk due to higher energy requirements associated with declining lung function, increased work of breathing, recurrent respiratory exacerbations and sepsis. Supplementary nutritional support via NG or gastrostomy feeding may be required to optimise nutritional status while waiting for a transplant. For some people consideration for transplantation is often a motivating factor to try to improve their nutritional status.

6.6.2 Good practice points

- Nutritional status should be optimised pre-transplant.

6.6.3 Post-transplant

Appropriate nutritional support should be provided in the acute post-transplant period to maintain nutritional status. In the majority of cases post-transplant energy requirements decrease due to a reduction in episodes of respiratory exacerbation and normalisation of the work of breathing. Nutritional status needs to be closely monitored and BMI should be kept within normal range (20–25kg/m2). A reduction in dietary energy intake and healthier eating practices may be required to achieve this.

Following a lung transplant education should be provided by the transplant team about food hygiene and safety. There is a risk of drug-nutrient interactions due to complex post-transplant medication regimens in particular grapefruit juice needs to be avoided as it interferes with the absorption of the immunosuppressive drugs Cyclosporin and Tacrolimus.

Other post-transplant complications that may require nutritional intervention include hypertension, osteoporosis, hyperlipidemia,[331] diabetes, nephrotoxicity and GORD.[332] Doses and levels of fat soluble vitamins should be monitored annually post-transplant as increased vitamin A and E levels have been observed [189]. Distal intestinal obstruction syndrome is also common in the early post-operative period and early medical intervention is essential.[333]

6.6.4 Good practice points

- Nutritional status should be closely monitored and advice tailored to changes in clinical and physical requirements.
- Good food hygiene and food safety practices should be adopted post-transplant.
- Fat soluble vitamin levels should be measured annually post-transplant and vitamin doses adjusted accordingly.
- CFRD should be screened for post-transplant and in those people with CFRD blood glucose control should be optimised.

6.7 Sports nutrition

There are currently no structured guidelines or evidence for sports nutrition recommendations in CF. Exercise is beneficial in CF as it aids mucus clearance, improves muscle strength, enhances bone mineral density, can improve appetite and promotes overall wellbeing. Exercise is therefore recommended in CF.[334]

Regular exercise is likely to increase energy requirements and it is therefore important to increase oral intake to ensure no muscle or weight loss occurs. Extra energy requirements are dependent on the intensity, duration and frequency of the exercise. Muscle gain is due to resistance and strength training along with a sufficient oral intake and is not due to the amount of protein consumed. Optimal oral intake will provide sufficient protein and there is no need to encourage high protein sports drinks.

Advice should be given to increase both fluid and salt intake during and after exercise due to fluid loss associated with sweating. The use of isotonic fluids and salt tablets may need to be considered.

The use of creatine supplements have been shown to increase work capacity with small repetitive exertion in a pilot study in people with CF.[335] However risks of dehydration and renal problems were anecdotally reported. Creatine supplementation is not recommended particularly in people under the age of 18 years.[336] Further research in people with CF is required.[335]

6.7.1 Good practice points

- Encourage exercise to promote optimal nutritional status and well being.
- Assess each individual patient and exercise regimen to ensure optimal and relevant energy intake.
- Ensure adequate hydration and sodium intake pre, during and post exercise.
- Creatine is not recommended.

7.0 CF related co-morbidities

7.1 Bone health

Low bone mineral density (BMD) in CF is thought to occur as a result of suboptimal peak bone mass accrual during childhood,[337] with premature low BMD due to reduced bone formation.[338] Increased bone resorption can also occur.[339] Reduced bone mineral density is more common in adolescent and adults with CF,[210,337,340,341] although it can occur in children.[342]

7.1.1 Risk factors

Risk factors for bone loss include poor nutritional status, vitamin D, vitamin K and calcium deficiencies, hypogonadism, glucocorticoid use, physical inactivity, CFTR dysfunction and infective pulmonary exacerbations.[200,211,343] To a lesser extent deficiencies of copper, phosphorous, magnesium, zinc, essential fatty acids and protein and an excess of vitamin A may also have aetiological roles.[210]

Low bone mineral density predisposes to an increased risk of fragility fracture. In a recent systematic review the pooled prevalence of vertebral fractures was 14 percent [344] which despite the younger age of the CF population, is comparable to that reported among untreated post-menopausal osteoporotic women.[345] Rib and thoracic vertebral compression fractures can have adverse effects on lung health in CF, as pain can impair effective airway clearance. In addition, severe osteoporosis is considered a relative contraindication to lung transplantation.[330]

7.1.2 Monitoring

Prevention and recognition of low BMD are important parts of routine CF care. Monitoring of bone health using dual energy X-ray absorptiometry (DXA) scans is recommended from the age of eight to ten years, with repeat scans every one to five years depending on the result and presence of risk factors.[196,200,210,211]

7.1.3 Prevention and treatment

A focus on minimising risk factors should be established during infancy, childhood and adolescence and continue into adult life. Particular attention should be given to achieving a normal nutritional status (see section 3.0) and optimising vitamin D, vitamin K1 and calcium intakes (see section 5.0). Weight bearing exercise for 20 minutes two to three times per week is recommended.

Bisphosphonate therapy is recommended for adults with CF with low trauma fracture and/or a BMD Z or T-score of less than -2 or bone loss at a rate of greater than 4% per year despite correcting any underlying deficiencies in vitamin D or calcium.[200] Earlier initiation of bisphosphonates should be considered (at a BMD Z or T-score of less than -1.5) if awaiting solid organ transplantation or if starting a prolonged course of oral glucocorticoids (greater than 3 months).[200] Vitamin D status and calcium intakes must be optimised before commencing bisphosphonate treatment. Careful consideration should be given to prescribing bisphosphonates in women of childbearing age.

7.1.4 Good practice points

- The aim of the nutritional management of bone health is to optimise factors that can affect bone health to enable people with CF to reach a normal peak bone mass. This is particularly important during puberty.
- Monitoring of bone health using dual energy X-ray absorptiometry (DXA) scans is recommended from the age of eight to ten years, with repeat scans every one to five years depending on the result.
- Particular attention should be given to achieving normal nutritional status.
- Vitamin D levels should be checked at least annually. Consensus guidelines recommend levels of 20–30ng/ml (50–75nnmol/l).
- Dietary calcium intake should be assessed regularly and a high calcium diet promoted.
- Vitamin K1 supplementation is recommended for all people with pancreatic insufficiency.

7.2 Cystic fibrosis-related diabetes (CFRD)

Cystic fibrosis-related diabetes is the most common co-morbidity in CF, affecting 20 percent of adolescents and 40–50 percent of adults over the age of 30 years.[126,346] The diagnosis of CFRD results in an additional treatment burden and individuals many need additional support to manage this aspect of their care.

Whilst CFRD shares features of Type 1 and Type 2 diabetes it is a distinct clinical entity. Cystic fibrosis-related diabetes is associated with deterioration in clinical status and contributes to poor nutritional status, decreased lung function, more frequent hospital admissions and increased mortality.[319,346,347] Early diagnosis and treatment have recently been associated with a decline in mortality rates in CFRD.[346,348]

7.2.1 Monitoring

Cystic fibrosis-related diabetes is part of a continuum of abnormalities in glucose tolerance, with only a few people with CF having completely normal glucose tolerance; there is movement along the glucose tolerance spectrum depending upon clinical status. Annual oral glucose tolerance tests (OGTT) for all people with CF from the age of 10 years are currently recommended to screen for CFRD.[20] However serial blood glucose monitoring or continuous glucose monitoring systems (CGMS) are essential when assessing the need for treatment.

7.2.2 Treatment

The aims of CFRD treatment are to maintain growth and optimise nutritional status, achieve good blood glucose control and avoid long-term diabetic complications.

Insulin is the recommended treatment of choice for people with CFRD as insulin deficiency is believed to be the primary cause of CFRD. Optimising glycaemic control improves nutritional status and pulmonary function, reduces mortality[349] and the development of long-term diabetic complications.[350,351]

Various insulin regimens are used in the treatment of CFRD these, should be tailored according to individual requirements taking into account their clinical and nutritional status, appetite and level of physical activity. A detailed dietary review should be conducted and advice given on a diet appropriate to meet individual nutritional requirements. People with CFRD should be advised that dietary advice, as recommended for people with type 1 or type 2 diabetes is not usually appropriate.[319,352] Some people with CFRD may be taught carbohydrate counting and to adjust their insulin doses according to their carbohydrate intake. This is particularly useful if they have variable eating habits. However if they do not carbohydrate count they should be encouraged to have regular meals containing complex carbohydrates and to limit their simple carbohydrate intake to meal times. Insulin regimens will need to be modified to optimise overnight glycaemic control in people with CFRD receiving supplementary enteral tube feeds.

Insulin requirements may vary according to evolution of CFRD, clinical status and treatments e.g. steroids and therefore continual assessment and monitoring are essential. People with CFRD should also receive an appropriate CFRD education package to manage all aspects of their diabetes. A collaborative multidisciplinary approach between CF specialists and a diabetes team that is familiar with CFRD and its unique features is advised.[20,319]

7.2.3 Good practice points

- Annual OGTT to screen for CFRD should begin by the age of 10 years in all people with CF who do not have CFRD.
- Optimise blood glucose levels to achieve normal growth and nutritional status and reduce the risk of long-term diabetic complications.
- Insulin and individualised dietary education is the recommended treatment for CFRD.
- Insulin regimens should be tailored to individual requirements and eating patterns.

7.3 Constipation

Constipation, defined as a reduced stool frequency and increased consistency often in association with abdominal pain and distension, is known to occur in people with CF although the exact incidence is unknown.[353] The exact aetiology is unknown although it is thought to be associated with altered intestinal fluid.[354] It is commonly thought to be associated with higher doses of PERT although one study found no correlation between PERT and constipation[355] and a more recent study showed that constipation was more frequently associated with a lower fat absorption.[353] In the same study there was no association with fibre and fluid intake and a similar finding for fibre has previously been noted in a previous study.[356] Diagnostic differentiation between DIOS and constipation is very important. Polyethylene glycol appears to be an effective treatment for constipation in CF and it appears not to have the side effects, including flatulence and abdominal cramps, that occur with lactulose.[357]

7.4 Distalintestinal obstruction syndrome (DIOS)

Distal intestinal obstruction syndrome is a common complication affecting adults and children with CF.[358] Prevalence has been reported to be between 5–12 episodes per 1000 patients per year in children[359] and up to 18 percent of adults with CF are affected.[360] Distal intestinal obstruction syndrome is a unique feature of CF and is characterised by the accumulation of viscid mucofaecal material in the terminal ileum and caecum. It can present acutely with complete intestinal obstruction (with bilious vomiting) but more commonly, sub-acutely with abdominal pain and distension. A right lower quadrant abdominal mass is sometimes palpable on clinical examination and a plain abdominal film reveals faecal loading in the right lower quadrant.

Several factors are thought to predispose to DIOS which include defective CFTR function leading to reduced chloride and fluid secretion into the gut lumen, enhanced fluid uptake, loss of bile salt triggered secretion in the terminal ileum, impaired gut motility and fat malabsorption.[361] The majority of people with

CF who present with DIOS are PI although DIOS can occur in those who are PS.[362] Risk factors which further predispose to DIOS include poorly controlled fat malabsorption, dehydration, previous episodes of DIOS and lung transplantation.[361]

In the majority of cases the clinical history and examination are sufficient to establish a diagnosis of DIOS. However uncharacteristic or protracted symptoms or failure to respond to treatment must trigger consideration of a differential diagnosis which includes; appendicitis, appendiceal abscess, intussusception, fibrosing colonopathy, inflammatory bowel disease and malignancy.[361]

There are few randomised controlled trials to guide management of this condition and treatment is largely empirical. Most people with CF and DIOS will respond to medical management.[363,364] Rehydration with either oral or IV fluids and administration of an osmotic laxative containing polyethylene glycol (PEG) such as Klean-Prep®, Movicol® or Laxido® or sodium meglumine diatrizoate (gastrografin) are usually effective . In more severe cases NG aspiration may be necessary and gastrografin enemas can be helpful.[361] Local installation of gastrografin in the caecum by colonoscopy is sometimes indicated in refractory cases.[365,366] Surgical treatment should be avoided if at all possible. A full dietary review should be conducted and modification to PERT dose initiated if there is evidence of under or overdosing of PERT. Avoidance of dehydration is important to prevent future episodes occurring and advice on maintaining an adequate fluid intake should be given.

7.4.1 Good practice points

- Appropriate medical management should be initiated and regularly reviewed.
- The importance of maintaining adequate hydration and fluid intake should be emphasised.
- All people with CF presenting with DIOS should be regularly reviewed by the Specialist CF Dietitian and PERT dosing should be optimised.

7.5 Liver disease

There is a wide spectrum of hepatobiliary complications arising in people with CF. These include steatosis (fatty liver) and focal or multilobular biliary cirrhosis, with most cases presenting in childhood or the early teenage years. Liver steatosis is the most common finding, affecting 23–75 percent of people with CF.[367,368] It has not been shown that steatosis progresses to cirrhosis and is thus considered a relatively benign condition at present.369 Focal biliary cirrhosis leads to multilobular biliary cirrhosis and portal hypertension in around 5–15 percent of cases.[369–371] Liver failure is a late event occurring mainly in older children and adults.

Ursodeoxycholic acid (UDCA) is the only available therapeutic option and is widely used to treat cystic fibrosis liver disease (CFLD). Treatment with UDCA has been shown to result in improvements in biochemical profile and a delay in the progression of liver disease when started early.[372] However it remains unclear whether UDCA improves outcomes such as the development of portal hypertension, cirrhosis, improvement in nutritional status, need for liver transplant or death.

Malnutrition is a common problem in people with CFLD. Body mass index is not a reliable indicator of nutritional status in people with advanced CFLD, who have ascites or oedema, and the use of more objective methods of nutritional assessment such as mid-arm circumference (MAC), mid-arm muscle circumference (MUAC), triceps skinfold thickness (TSF) and handgrip should be considered. Dry weight should be used if ascites or oedema are present.

People with CFLD may have a further 20–40 percent increase in their energy requirements, as cholestasis and cirrhosis are associated with increased oxygen consumption. In addition cholestasis and inadequate bile acid secretion are associated with fat malabsorption.[373] An important component of the management of CFLD therefore, is maintaining optimal weight and nutritional status. To reduce the possible risks of hepatic encephalopathy special considerations should be given to the management of patients with end-stage cirrhosis which include: ensuring protein intakes do not exceed 1.8–2.0/kg per day, evenly distributing protein intake, meeting energy requirements and aiming for bowels to opened two to three times per day.[374,375]

Pancreatic enzyme dosing should be reviewed regularly to ensure optimal absorption of long chain triglycerides and essential fatty acids but it is important that there is awareness that some malabsorption may occur in advanced CFLD that is unresponsive to PERT. Care should be taken to ensure PERT doses are not escalated inappropriately. Enteral feeding may be indicated particularly in those awaiting liver transplant. Vitamin A levels should be interpreted with caution in advanced CFLD (see section 5.2.3). Liver transplantation is associated with improvements in nutritional status.[376–380]

7.5.1 Good practice points

- Maintenance of optimal weight and nutritional status is the mainstay of nutritional intervention for people with CF liver disease.
- Protein requirements should not be exceeded in people with end-stage cirrhosis.
- In the presence of ascites or oedema dry weight should be used.
- Enteral tube feeding may be indicated to maintain adequate nutritional status particularly in those awaiting liver transplantation.

7.6 Renal disease

Renal disease is not considered a primary manifestation of CF although the CFTR protein abnormality is expressed in renal tubule cells.[381] Chronic kidney disease (CKD) tends to occur as a result of treatment with nephrotoxic drugs such as aminoglycosides, non-steroidal analgesic agents and immunosuppressive therapy.[382,383] Cystic fibrosis-related diabetes requiring insulin is an additional risk factor for the development of CKD in adults with CF, the risk increasing with duration of CFRD, especially among individuals with evidence of microalbuminuria.[384] A recent study estimates an overall prevalence of moderate-to-severe CKD of two percent in the adult CF population[384] with age-specific prevalence rates two to three times higher than in the general population.[385] People with CF are also at increased risk of renal stones,[386] the most common being calcium oxalate.[381] Monitoring of renal function is important in CF especially in those on frequent courses of intravenous antibiotics or immunosuppressive therapy. Dietary modifications are rarely required except for in those people with CF who are on dialysis.

7.7 Gastro-oesophageal reflux disease (GORD)

Gastro-oesophageal reflux disease (GORD) is a common condition where the stomach contents pass back up into the oesophagus through the gastro-oesophageal junction. Gastro-oesophageal reflux disease is a frequent problem in CF, where symptoms such as heart burn or regurgitation of food occur and these can impact on daily life.[387–389]

7.7.1 Risk factors

Gastro-oesophageal reflux occurs more frequently in infants compared to older children and adults partly due to physiological factors such as a short, narrow oesophagus and underdevelopment of the oesophageal sphincter (see section 3.4.4). Several factors are thought to account for the increase in GORD in the older child or adult which include a depressed diaphragm from hyper-inflated lungs, increased cough (causing increased intra-abdominal pressure), lower oesophageal sphincter pressure and medications such as aminophylline and salbutamol.[390,391]

7.7.2 Monitoring

In young children GORD can cause food aversion and subsequent eating problems. In adults GORD is associated with poor appetite and can lead to oesophagitis and Barrett's oesophagus. Oesophagitis is also associated with iron deficiency anaemia due to low level chronic blood loss from the inflamed lower oesophagus. Most infants will show obvious signs of GORD with vomiting, posseting and occasional rumination but GORD should also be considered in infants with faltering growth, or those who experience discomfort or pain despite adequate PERT. Asymptomatic GORD is common in CF and older children and adults should specifically be asked about symptoms of heartburn or regurgitation.

7.7.3 Treatment

A trial of antacid medication in the form of a proton pump inhibitor (PPI) such as omeprazole or lansoprazole is recommended as the first line therapy for GORD.[392] In severe disease an H2-receptor antagonist may be added as it modifies acid production by a different mechanism. Pro-motility drugs can also be considered; taking into account recent Medicines and Healthcare Product Regulatory Agency recommendations.[393] There is no evidence that feed thickeners work although a small RCT suggested that the oesophageal height of the episodes of reflux was significantly reduced.[394] Raising the head of the child's bed or cot may reduce clinical symptoms of reflux. People with CF who do not respond to empirical treatment with a PPI should undergo further investigation for GORD prior to further treatment. This is particularly relevant in people with CF who experience prolonged symptoms because of the increased incidence of digestive tract cancers at the oesopho-gastric junction.[395]

Surgical intervention with fundoplication is occasionally used to control symptoms in people with CF not controlled by medical management. A recent study has shown a reduction in pulmonary exacerbations and less of a decline in lung function, in addition to significant improvements in weight in people with CF who underwent a Nissen's fundoplication.[396]

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The Cystic Fibrosis Trust is the only UK-wide charity dedicated to fighting for a life unlimited by cystic fibrosis (CF) for everyone affected by the condition. Our mission is to create a world where everyone living with CF will be able to look forward to a long, healthy life.

At the Trust we are:

- Investing in cutting-edge research
- Driving up standards of clinical care
- Providing support and advice to people with CF and their families
- Campaigning hard for the issues that really matter

Fighting for a Life Unlimited