# NUTRITIONAL MANAGEMENT OF CYSTIC FIBROSIS

CYSTIC FIBROSIS TRUST

UK Cystic Fibrosis Trust
Nutrition Working Group

April 2002

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ISBN 0-9540536-5-6

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**The Cystic Fibrosis Trust UK thanks the members of the Nutrition Working Group and all the Contributors for their help in compiling this report.**

# NUTRITIONAL MANAGEMENT OF CYSTIC FIBROSIS
# A CONSENSUS REPORT

## CONTENTS

# FOREWORD

This is one of a series of documents from the Cystic Fibrosis Trust describing what consensus groups consider to be best clinical practice in various aspects of cystic fibrosis (CF) treatment.

The document is intended for all health care professionals working with people who have cystic fibrosis and their families.

The Nutrition Group recognises that practice will differ slightly between various Specialist CF Centres; this document represents what the present Nutrition Group and those who have contributed to the document consider to be best clinical practice at present.

We are grateful to the Directors of the UK Specialist CF Centres and Clinics and their dietetic colleagues for their valuable comments and suggestions.

Members of the Nutrition Working Group
April 2002

## Grading scheme for recommendations used in the Nutritional Management of Cystic Fibrosis

The criteria for the grading of recommendations in this document are based upon a paper by Petrie et al published on behalf of the Scottish Intercollegiate Guidelines Network.

### Levels of evidence

| *Level* | *Type of evidence (based on AHCPR, 1992)* |
|---|---|
| I a | Evidence obtained from meta-analysis of randomised controlled trials. |
| I b | Evidence obtained from at least one randomised controlled trial. |
| II a | Evidence obtained from at least one well designed controlled study without randomisation. |
| II b | Evidence for at least one other type of quasi-experimental study. |
| III | Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case controlled studies. |
| IV | Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. |

### Grading of recommendations

| *Grade* | *Type of recommendation (based on AHCPR, 1992)* |
|---|---|
| A (levels I a, I b) | Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation. |
| B (levels II a, II b, III) | Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of the recommendation. |
| C (level IV) | Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality. |

Petrie GJ, Barnwell E, Grimshaw J, on behalf of the Scottish Intercollegiate Guidelines Network. *Clinical guidelines: criteria for appraisal for national use.* Edinburgh: Royal College of Physicians, 1995.

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# 1. INTRODUCTION

## 1.1 Nutrition and survival

In the past, growth failure and weight loss were seen as inevitable in the face of progressive lung disease in patients with cystic fibrosis (CF). However, in the 1970s the Toronto CF Clinic was able to show that a high fat, high calorie diet promoted a normal growth pattern and improved survival (Corey et al, 1988 [III]). This approach to nutrition has been endorsed by most Specialist CF Centres and has resulted in an overall improvement in respiratory prognosis. Good nutritional status can be achieved in the majority of patients with CF by combining a high calorie diet with adequate pancreatin supplements. However, for some patients with CF, nutrition remains a problem.

## 1.2 Factors associated with poor nutrition

Poor nutrition in CF results from factors that are often interlinked:

- Increased stool energy losses.
- Anorexia and poor dietary intake.
- Increased energy demands of the disease.
- Abnormal adaptive response to malnutrition.
- Other factors.

### 1.2.1 Increased stool energy losses

Dietary advice on increasing energy intakes has become an important part of CF management. However, despite more effective pancreatin replacement therapy, increased energy losses in the stools may still contribute towards an energy deficit sufficient to limit growth (Murphy et al, 1991 [IIb]).

### 1.2.2 Anorexia and poor dietary intake

Deficient intake is often the chief reason for growth failure in patients with CF lung disease. During pulmonary exacerbations energy requirements increase to meet the immune response to infection, yet the appetite usually diminishes. Subsequent dietary intake is often inadequate. Thus, in children, catch up growth is often incomplete leading to a familiar pattern of slow weight gain punctuated by acute step-like episodes of weight loss associated with further chest infections. In adults there may be a progressive pattern of weight loss, leading to a reduction in respiratory muscle strength and subsequently, impaired lung function.

### 1.2.3 Increased energy demands of the disease

The energy needs of patients with CF vary widely and have been stated as 120-150 percent of those required by healthy individuals of the same age, sex and size (Pencharz et al, 1984 [IIb]; Vaisman et al, 1987a [IIb]). This reflects an increase in the basal metabolic rate (BMR), which, in sedentary adults accounts for three-quarters of daily energy expenditure. In the CF lung, a combination of obstructive and restrictive changes increases the work of breathing and thus the BMR by 30% (Levison & Cherniak, 1968 [IIb]). This figure approximates with more extensive studies in adults with chronic bronchitis and emphysema where the resting energy expenditure is increased to 140% predicted. Infection and inflammation also has an energy cost (Bell et al, 1996 [IIb]).

An increased energy requirement at the cellular level has also been proposed (Shepherd et al, 1988 [III]), although recent data collected from babies with cystic fibrosis strongly suggest that this is not the case, and previous data were confounded by subclinical lung disease. These factors emphasise the need for individual assessment of the energy requirements for every patient.

### 1.2.4 Abnormal adaptive response to malnutrition

The adaptive response to malnutrition in CF lung disease may also be abnormal (Miller et al, 1982 [III]). In the normal child, even with a degree of malnutrition, the response to infection is an increase in protein synthesis. Some children however, exhibit a marked decrease in protein synthesis with acute pulmonary infection. Stable but chronically infected patients have also been shown to be in a state of protein catabolism, and will therefore tolerate acute infections poorly. In malnourished children stunting may be seen despite a maintained calorie intake, reflecting the increased work of breathing associated with unrecognised respiratory infection.

### 1.2.5 Other factors

Treatment may also be a factor in increasing energy demands by as much as 10%, as Vaisman et al demonstrated by studying the effects of salbutamol, a β agonist, on heart rate and resting energy expenditure (Vaisman et al, 1987b [IIb]).

## 1.3 Can nutrition be improved?

The encouragement of a high calorie, high protein diet will produce adequate growth in the majority of children and adults with cystic fibrosis. In other cases an improvement in nutrition can be achieved by simple means including the use of pre-mixed and powdered dietary supplements. In patients with more severe lung disease, anorexia is often the chief problem leading to malnutrition. In such patients taste fatigue may lead to oral supplements being rejected. Under these circumstances some form of invasive nutritional intervention is necessary. Significant weight gain and an improvement in pulmonary function have been achieved, in both the short and long-term, by providing supplementary nutrition. Simple techniques such as nasogastric feeding with bolus or overnight feeds should be considered as short-term solutions. Long-term supplementation via both gastrostomy and jejunostomy has also produced either acceleration in growth velocity or improved weight for height (Steinkamp & von der Hardt, 1994 [III]).

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# 2. ASSESSMENT OF GROWTH AND NUTRITIONAL STATUS

## 2.1 Introduction

With modern treatment a normal nutritional status and rate of growth should be achievable goals for the majority of patients with cystic fibrosis. The following section gives detailed information of how growth should be monitored and how growth failure should be defined in cystic fibrosis.

## 2.2 Methods of assessment

### 2.2.1 Weight, height and head circumference

There must be accurate and sequential measurements of weight, height and in children under 5 years old, head circumference. Methods used for assessment must be consistent and performed by experienced staff. These measurements should be recorded on the appropriate centile charts. These charts are compiled from cross-sectional surveys of childhood populations. Between 0 and 18 years weight and height measurements should be plotted on the 1990 Nine Centile United Kingdom Charts (Freeman et al, 1995 [III]; Preece et al, 1996 [III]). Because growth patterns have changed, these charts have replaced the Tanner-Whitehouse charts first published in 1966 (Tanner et al, 1966a [III]; Tanner et al, 1966b [III]). Patients with CF often experience delayed puberty (Weltman et al, 1990 [III]), which must be taken into consideration when interpreting growth progress, as plotted on centile charts. Care must also be taken when interpreting head circumference centiles as infants and young children with CF have been shown to have a smaller head circumference than controls (Ghosal et al, 1995 [IIb]). Centile charts also allow the determination of weight and height velocity so that any slowing in weight gain or growth can be easily picked up. Weight and height velocity charts help to provide a greater sensitivity to the assessment if growth is poor.

In the interpretation of growth charts genetic short stature must be taken into consideration. The interpretation of malnutrition and growth failure during adolescence may also be affected by delayed puberty and growth spurts during this period (Landon & Rosenfeld 1984 [III]; Byard 1994 [III]). Delayed puberty has been documented in patients with CF who have significant nutritional problems (Weltman et al, 1990 [III]) and in those who are well nourished (Johannesson et al, 1997 [III]). This may result in an over estimate of malnutrition in this age group. Children with delayed puberty will initially lose centiles but should catch up when they enter their delayed puberty and their growth accelerates. Noting stages of breast, pubic hair and genital development and recording age of menarche in girls are important in assessing the stage of development (Tanner & Whitehouse, 1976 [III]).

### 2.2.2 Body Mass Index/Quetelet Index

This assessment is simple to perform and easy to undertake in routine clinical practice.

The body mass index (BMI) (weight [kg]/height [m]$^2$) is widely used to assess the nutritional status of adult patients with cystic fibrosis. BMI assesses whether weight is in proportion to height and therefore gives an indication of body fatness or thinness. Recently it has also been validated for children (Prentice, 1998 [IIb]), and BMI values for children with CF in the UK have been reported (Morison et al, 1997 [III]). Although BMI centile charts are now available (Cole et al, 1995 [III]) care must be taken in their interpretation. Inaccurate assessment can follow in children whose height may have been adversely affected by chronic malnutrition and/or delayed puberty. Nonetheless, a recent Expert Consensus Group of the Royal College of Paediatrics and Child Health advised the use of BMI in preference to %wt/ht even for children (*www.rcpch.ac.uk* 2001 [IV]).

### 2.2.3 Percentage weight for age (%wt/age), height for age (%ht/age) and percentage weight for height (%wt/ht)

This method of assessment is often used in children in preference to BMI. The measurements are calculated either by using a Cole's growth assessment slide rule (Cole et al, 1981 [III]) or from a standard equation:

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

Serial %wt/age, %ht/age and %wt/ht measurements are useful in assessing growth progress in an individual patient or to compare data from a number of patients or patient groups. Like BMI, the %wt/ht, assesses whether weight is in proportion with height, but again it is not able to assess nutritional stunting or the effects of delayed puberty. In order to do this serial measurements of %wt/age and %ht/age must be considered together. Although the assessment is simple to perform and easy to undertake extreme care must be taken in performing the calculation as a high degree of inaccuracy has been reported in routine clinical practice (Poustie et al, 2000 [III]).

### 2.2.4 Weight, height and BMI standard deviation scores (Z Scores)

The use of this method of assessment has been mainly restricted to research, the scores being inconvenient to calculate in the clinic situation. A disk (compatible with Microsoft Excel) is now available from the Child Growth Foundation containing files that summarise the 1990 British Growth Reference Standards for height, weight, BMI and head circumference from infancy to adulthood. Standard deviation scores are a convenient way of assessing an individual's growth over a period of time and of comparing growth between groups of patients.

## 2.3 Assessment of body composition

### 2.3.1 Importance of measuring body composition

The growth assessment methods described above do not allow the determination of body composition. Determining body composition offers a more accurate assessment of nutritional status by evaluating the nature of malnutrition. It also allows determination of the response to nutritional therapy in terms of body composition. Measurements, which enable us to assess whether, weight loss or gain is mainly attributable to lean tissue, water or fat mass would affect the method of nutritional support chosen and also the type of nutrients delivered to the patient. Most methods of assessing body composition are based on a two-compartment model, dividing the body into fat and fat free mass. Methods include total body potassium (TBK), (Shepherd et al, 1989 [IIb]), total body electrical conductivity (TOBEC), bioelectrical impedance analysis (BIA), (Azcue et al, 1993 [IIb]; Pichard et al, 1999 [IIb]), total body water by isotope dilution (Shepherd et al, 1989 [IIb]), and dual energy x-ray absorptiometry (DEXA), (Slosman et al, 1992 [IIb], Rochat et al, 1994 [IIb]). Unfortunately, many of these techniques are invasive, expensive and extremely difficult to undertake in routine clinical practice. Their use is therefore restricted to research.

### 2.3.2 Skin fold thickness

Simpler methods of body composition assessment include simple straightforward anthropometric measurements to estimate body composition (Brook, 1971 [III]). Skin fold thickness relies on the reliability of subcutaneous fat folds to predict total body fatness. The reliability and reproducibility of this determination is poor in CF (Newby et al, 1990 [IIb]) and it is not therefore recommended in routine clinical practice.

### 2.3.3 Mid upper arm circumference

This gives an estimate of lean body mass. However again, the reliability of its use in CF is poor (Frisancho, 1981 [IIb]).

### 2.3.4 Bone age/skeletal age

Delay in skeletal maturity (Tanner & Whitehouse, 1976 [III]) increases with age as respiratory problems increase (Mearns, 1983 [III]). Estimation of skeletal age should form part of the assessment of any child with stunting (ht/age<90% or <0.4th height centile) or pubertal delay. Bone age should be estimated using the Tanner and Whitehouse (TW2) method (Bull et al, 1999 [IIb]). The delay in skeletal maturity is often surprisingly modest. In one series 20 percent of patients had a delay of less than one year and only 6 percent of over 2 years (Mearns, 1983 [III]).

### 2.3.5 Bone mineral density

Osteopenia and osteoporosis have both been reported in adults and children with cystic fibrosis (Gibbens et al, 1988 [IIb]; Rochat et al, 1994 [IIb]; Henderson & Madsen, 1996 [III]). With increasing life expectancy, the consequences of this problem on growth and development are of concern. Bone mineral density is assessed by DEXA (Slosman et al, 1992 [IIb]; Rochat et al, 1994 [IIb]). Although this is an expensive procedure, regular DEXA scans carried out at Specialist CF Centres, should be considered in all patients over the age of 10 years; further research will help to determine how often. Particular concern has been expressed over bone demineralisation following lung transplantation (Shane et al, 1996 [III]). Thus, candidates for lung transplantation should be evaluated for osteopenia and vitamin D deficiency at the time of acceptance to the transplant waiting list.

## 2.4 Frequency of assessment

### 2.4.1 Infants

Infants should attend the clinic at least every 2 weeks until they are thriving. The clinic visit must include nude weight, length and, ideally, head circumference measurements.

### 2.4.2 Older children

The frequency of follow up for older children varies. Height and weight (measured in consistent light clothing) should be recorded at each clinic visit, with 3 monthly measurements as a minimum. Height measurements should continue until skeletal maturity is reached and growth has ceased. Head circumference is also measured in some clinics.

### 2.4.3 Adults

Adult patients should have their weight recorded at each clinic visit. Likewise height measurements must be recorded until skeletal maturity is reached and there is no evidence of further growth. Then annual measurement should be performed.

### 2.4.4 Centile charts

Until growth has ceased all weight and height measurements and, if measured, head circumference should be plotted on appropriate charts.

### 2.4.5 Body mass index

The BMI should be calculated for all adult patients at each clinic visit.

### 2.4.6 %wt/age, %ht/age and %wt/ht

Should be calculated for children at their Annual Review at the Specialist CF Centre or CF Clinic.

### 2.4.7 Standard deviation scores for weight, height and BMI

Standard deviation scores (SDS) are currently more appropriate as research tools.

## 2.5 Defining growth failure

### 2.5.1 Different criteria and incidence

There is wide variation in the reported incidence of malnutrition in patients with CF between clinic and country populations. One factor contributing to this variability is the criteria and cut off points used to define poor growth and malnutrition. In addition, reference standards for growth differ between clinics and countries, and there is wide variation in sample populations, type of data collection and method of curve construction. This makes it difficult to make comparisons between different clinic populations.

In a recent study three different anthropometric standards were used to interpret the Canadian CF Registry data for 1994. All three (US National Centre for Health Statistics, the British Tanner and Whitehouse standards and a new British composite) gave different results and even ideal weight was not free from bias (Shin et al, 1997 [III]). For consistency in the UK the 1990 British Growth Reference values should be used (Freeman et al, 1995 [III]).

### 2.5.2 Age related definition of nutritional/growth failure

| | |
|---|---|
| Child <5 years | wt/ht <85%<br>weight loss or plateau in weight gain over two clinic visits (maximum interval 4 months). |
| Child 5 -18 years | wt/ht <85%<br>weight loss over two clinic visits (maximum interval 6 months)<br>plateau in weight over two clinic visits (maximum interval 6 months). |
| Adult | BMI <19<br>wt loss >5% body weight for >2 months' duration. |

## 2.6 Criteria for different stages of nutritional intervention

| | *<5 years* | *5-18 years* | *>18 years* |
|---|---|---|---|
| **Normal nutritional state -** ***Preventative counselling*** | wt/ht 90-110% | wt/ht 90-110% | BMI 19-25 and/or no recent weight loss |
| **Dietetic referral indicated -** ***Consider supplements*** | wt/ht 85-89% or weight loss over 4 months or plateau in weight over 6 months | wt/ht 85-89% or weight loss over 6 months or plateau in weight over 6 months | BMI <19 or 5% weight loss over > 2 months |
| ***Aggressive nutritional support*** | Supplements tried and either - wt/ht <85% or weight falling 2 centile positions | Supplements tried and either - wt/ht <85% or weight falling 2 centile positions | Supplements tried and either - BMI <19 or >5% weight loss over >2 months |

For all age categories pay special attention if stunting is evident, defined as *ht/age of <90% or height centile < 0.4$^{th}$.*

## 2.7 Techniques for measuring growth

Techniques for measuring growth are well described in *Buckler JMH. A Reference Manual of Growth and Development. 2$^{nd}$ ed. Oxford: Blackwell Science, 1997.*

All 1990 Nine Centile United Kingdom Charts are published by the Child Growth Foundation (2 Mayfield Avenue, London W4 1PN) and are available from Harlow Printing, Maxwell Street, South Shields, Tyne & Wear, NE33 4PU.

## 2.8 Recommendations

- ***Weight should be recorded at every clinic visit. [C].***
- ***In children height should be recorded at every clinic visit. In adults height should be recorded at every clinic visit until growth has ceased and then annually [C].***
- ***Head circumference should also be recorded for infants and some centres also advise for children less than 5 years of age [C].***
- ***Until growth has ceased measurements should be recorded on the appropriate centile charts [C].***
- ***Pubertal delay should be taken into consideration when interpreting growth data [C].***

- *In children where there is concern about nutritional status, and at the Annual Review, measurements should also be converted to percentage weight for height and percentages weight and height for age and body mass index to allow greater accuracy in the determination of nutritional status [C].*
- *For adults, measurements should be converted to body mass index [C].*
- *Assessment of bone mineral density by DEXA should be considered as part of patient monitoring after 10 years of age, and should be performed in patients referred for heart/lung and double lung transplantation[C].*

## 2.9 Appendix - Some reported growth definitions

**1) USA consensus report (Ramsey et al, 1992 [IV])**

| | | |
|---|---|---|
| %wt/ht | >110% | overweight |
| | 90-110% | normal |
| | 85-89% | underweight - requires dietetic referral |
| | 80-85% | early malnutrition - aggressive nutritional support |
| | 75-80% | moderate malnutrition |
| | <75% | severe malnutrition |

*If height <3rd centile - "stunting" - pay special attention*

**USA Definition of growth failure**

| | | |
|---|---|---|
| i) | <5 years | wt/ht <85%<br>weight loss for 2 months<br>plateau in weight for 2-3 months |
| ii) | 5-18 years | wt/ht <85%<br>weight loss for >2 months<br>plateau in weight for 6 months |
| iii) | >18 years | wt/ht <85%<br>weight loss of > 5% of usual weight for > 2 months duration |

**2) USA - Evaluation of various criteria to define malnutrition (Lai et al, 1998 [III])**

Malnutrition was defined by 4 criteria; however, there was a significant discrepancy when different criteria were used to distinguish "stunting" versus "wasting" in malnourished children with cystic fibrosis.

i) ht/age <5th centile (stunting)
or
wt/age <5th centile (wasting)

ii) ht/age < 90% of reference median
or
wt/age <80% of reference median

iii) ht/age <5th centile
or
% ideal wt/ht <85%

iv) ht/age <90% of reference median
or
wt/ht<85% of reference median

**3) Waterlow's classification of nutritional status (Waterlow et al, 1977 [IV])**

| | | |
|---|---|---|
| ht/age | <90% | stunting |
| wt/ht | <80% | wasting |

**4) The World Health Organisation (WHO, 1986 [IV])**

3rd percentile or -2SD below mean = malnutrition

**5) BMI - Adult classification (WHO, 1998 [III])**

| | |
|---|---|
| <18.5 | underweight |
| 18.5-24.9 | ideal |
| 25-29.9 | overweight |

**6) Table.**
**Association of standard deviation score (SDS) with centile position**

| SDS | Wt/age | Ht/age | BMI (adult) | |
|---|---|---|---|---|
| | | | male | female |
| -3SD (0.13$^{th}$ centile) | 75 | 90 | | |
| -2SD (2.28$^{th}$ centile) | 80 | 95 | 18 | 17 |
| -1SD (15.87$^{th}$ centile) | | | 19.5 | 19 |
| 0SD (50$^{th}$ centile) | 100 | 100 | 22 | 21.5 |
| 1SD (84.14$^{th}$ centile) | | | 25 | 26.5 |
| 2SD (97.72$^{th}$ centile) | | | 29 | 29 |
| 3SD (99.87$^{th}$ centile) | 135 | 115 | | |

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# 3. NUTRITIONAL MANAGEMENT

## 3.1 Introduction

Nutritional requirements are increased in cystic fibrosis, reflecting the energy demands of progressive lung disease plus malabsorption of protein and fat secondary to exocrine pancreatic insufficiency. The importance of maintaining growth and nutrition in patients with CF is well established (Corey et al, 1988 [III]). Studies have demonstrated links between weight gain and survival, and have shown a slower rate of deterioration in lung function in pancreatic sufficient patients when fat excretion is normal (Gaskin et al, 1982 [III]). However, reports suggest that many children struggle to meet these higher requirements. Hypoalbuminaemia, sub-optimal vitamin and essential fatty acid status and reduced body fat and lean tissue have all been reported (Marcus et al, 1991 [III]; Sokol et al, 1989 [III]; Greer et al, 1991 [III]).

Early and severe nutritional and growth problems occur in the majority of untreated infants with cystic fibrosis. Fat malabsorption, mainly as a result of exocrine pancreatic insufficiency, is seen in 95% of the UK CF population. Despite pancreatic enzyme replacement therapy intestinal fat absorption remains sub-optimal and patients also require daily supplementation with fat-soluble vitamins. Infants with CF may therefore have increased energy requirements due to incompletely controlled malabsorption. Early diagnosis following neonatal CF screening provides an opportunity to prevent these nutritional problems in infancy (Bronstein et al, 1992 [III]; Farrell et al, 1987 [Ib]). It is therefore essential that attention be given to both the quantitative and qualitative aspects of nutrition from diagnosis.

## 3.2 Nutritional requirements from birth

### 3.2.1 Infants with CF can achieve normal growth

Case-controlled studies suggest that appropriate growth rates can be achieved in infants with CF, whether receiving hydrolysed formulae, standard formulae or breast milk (Farrell et al, 1987 [Ib]; Holliday et al 1991 [III]; Simmonds et al, 1994 [III]; Farrell et al, 1997 [Ib]; Ellis et al, 1998 [Ib]. Farrell et al, 2001 [Ib]).

### 3.2.2 Type of feed

Breast milk or whey-based artificial formulae (according to parental preference) are suitable from birth for the infant with CF who is diagnosed following neonatal screening. However, specialised nutritional modification involving energy supplementation, protein hydrolysate, or nasogastric feeds may be required in infants with growth failure. Those who have had small bowel surgery for meconium ileus, with consequent loss of small bowel surface area, may require a protein hydrolysate (pre-digested) feed, such as Pregestimil, PeptiJunior or Prejomin.

## 3.3 Breastfeeding

### 3.3.1 Advantages of breastfeeding

Breast milk has many real and potential advantages for infants with cystic fibrosis (Slusser & Powers, 1997 [IV]; Henschel & Inch, 1996 [IV]):

- The lipase and amylase content may partially compensate for diminished pancreatic secretion in the infant with cystic fibrosis.
- Immunological properties (including immunoglobulins, lactoferrin, epidermal growth factor and lysozymes) may offer some protection against infection and the development of cows' milk protein allergy.

- An optimal fatty acid profile may maintain/improve plasma essential fatty acid status.
- The presence of taurine, which is necessary for bile salt synthesis, may enhance fat absorption.
- Optimal bioavailability of nutrients, including iron, protein, and calcium.
- Psychologically beneficial to the mother.

#### 3.3.2 Most women are capable of breastfeeding

The World Health Organisation recognises that the vast majority of women (97% or more) are physiologically capable of breastfeeding their babies successfully. The majority of women in the UK (64%) now choose to breastfeed, however only a few (26%) are still breastfeeding at four months (OPCS, 1985 [III]). A 1996 review of infant feeding practices in the UK suggests that only a small proportion of babies with CF continue to be breastfed at 3 months of age (Wolfe, 1998 [IV]). *"...The discrepancy between those who are capable and those who succeed may pinpoint weaknesses amongst those who support them rather than the women themselves..."* (Raj & Plichta, 1998 [IV]).

#### 3.3.3 Resources necessary

Staff training and access to midwives or lay breastfeeding organisations (National Childbirth Trust or La Leche League breastfeeding counsellors) should ideally be available to provide informed support. A good understanding of the basic principles of lactation together with adequate support for the breastfeeding mother is required for success (RCM, 1991 [III]). Breastfeeding is a hormonally controlled supply and demand process; the more the infant suckles, the more milk will be produced. Slow weight gain can be corrected by increasing feeding frequency.

### 3.4 Bottle-feeding

#### 3.4.1 Type of formula feed

Women who wish to bottle-feed their infants also require support in their feeding choice. The use of a whey-based artificial formula is recommended. There is no evidence to suggest that switching brands of formula is of any benefit to the baby; indeed the "hungry" baby is to be encouraged to feed, on demand, in order to meet the increased energy requirements; intakes of formula in excess of 200 ml/kg are not unusual.

#### 3.4.2 Cows' milk intolerance

Persisting gastrointestinal symptoms and signs despite enzyme therapy may be indicative of cows' milk protein allergy or lactose intolerance. The incidence of cows' milk intolerance in one series of infants with CF in the UK has been reported at 8% (Hill et al, 1989 [IV]). A protein hydrolysate formula should be used in view of the possibility of developing additional soya intolerance.

### 3.5 Pancreatic enzyme replacement therapy

#### 3.5.1 Pancreatin started after evidence of malabsorption

Pancreatic enzyme replacement therapy (PERT) should be introduced once there is evidence of intestinal malabsorption. Clinical signs include fatty stools and poor weight gain. However, steatorrhoea should be confirmed by direct microscopy for fat globules (Walters et al, 1990 [IIb]) and pancreatic insufficiency by measurement of faecal pancreatic elastase-1. This latter test appears simple and reliable with concentrations <100 µg/g indicative of severe pancreatic insufficiency (Cade et al, 2000 [IIb]). Approximately 92% of infants with CF have pancreatic insufficiency by 1 year of age (Bronstein et al, 1992 [IIb]). Adequate PERT is necessary to avoid high faecal energy

losses. Individual requirements vary widely which may reflect differing degrees of residual pancreatic function, the type of enzyme preparation and patho-physiological factors such as intestinal pH (Littlewood & Wolfe, 2000 [IV]). Dietary fat provides approximately 50% of the energy intake of young infants; thus, inadequate control of fat absorption can have a devastating effect upon nutritional status.

### 3.5.2 Method of administration

Enteric-coated enzyme granules, microspheres or minimicrospheres can be administered via a teaspoon at intervals throughout the feed (mixed with a little milk or pureed fruit). They should be given to all pancreatic insufficient infants, irrespective of the milk used including those fed on protein hydrolysate formulae. They are well tolerated by young infants and more effective at controlling symptoms of malabsorption than older powdered preparations (Beverley et al, 1987 [IIb]). Early introduction also allows the child to become accustomed to the granular preparation, avoiding the difficulties associated with introducing new treatments to young children.

### 3.5.3 Recommendations for pancreatic enzyme supplementation

- *Acid resistant pancreatin microspheres or minimicrosphere preparations are recommended for infants when intestinal malabsorption and pancreatic insufficiency are confirmed [B].*
- *Dosages should not exceed 10,000 IU lipase/kg bodyweight /day [B].*
- *Dividing the pancreatin dose between the beginning, middle and end of the feed may promote better mixing of pancreatin and chyme and can anticipate normal variations in appetite [B].*
- *Initial dosages of 1/4 standard strength capsule (5,000-10,000 IU lipase per capsule) per 60-120 ml formula feed, or per breastfeed, can be offered and individually titrated against symptoms of malabsorption [B].*
- *Enzymes should only be mixed with a small amount of food or liquid immediately before administration [B].*

## 3.6 Energy supplementation

If an infant is failing to thrive, despite adequate control of the malabsorption with pancreatic enzyme replacement therapy, energy supplements can be prescribed to boost the energy content of foods and fluids. Additional supplementation to infant formulae up to 8% carbohydrate or 4% fat will achieve an energy density of approximately 1 kcal/ml. A high-energy infant formula could be used if the infant is bottle-fed, but is perhaps less flexible and more expensive. A breastfed infant may need to be encouraged to feed more frequently. Not all infants with CF require energy supplementation. Individual assessment of need is required to avoid compromising the nutritional quantity and quality of the infant's diet.

## 3.7 Sodium supplementation

There is no evidence to suggest that infants with CF require routine sodium supplementation in the UK. However, it has been suggested that the sodium content of infant formulae may be inadequate in hot climates when sodium loss from the body is higher. Feeding 200 ml/kg/day of a standard infant formula provides 1.6 mmol/kg/day sodium, while the same volume of hydrolysed formula supplies 2.8 mmol/kg/day. In some infants with CF, growth problems may be exacerbated by poor dietary intake of sodium (MacDonald, 1996 [IV]). Sodium deficiency can be confirmed by a spot urine analysis ($Na^+ < 10$ mmol/l) and measurement of serum electrolytes; it can be corrected with sodium supplementation of 1 - 2 mmol/kg/day and the response monitored.

In hot weather, when supplements are advised, the following daily doses of sodium chloride are recommended - less than 1 year old 500 mg, 1-7 years 1 g, more than 7 years 2 to 4 g in divided doses (600 mg sodium chloride=10 mmol Na). *Dioralyte* sachets (R.P.R.) are a convenient preparation for younger patients, each sachet contains 350 mg of sodium chloride, also potassium, which may be beneficial.

## 3.8 Introducing solids in older infants

### 3.8.1 Age of weaning

Solid foods should be introduced between the ages of 4-6 months, according to the UK Committee on Medical Aspects of Food Policy (COMA) guidelines (Department of Health, 1991 [IV]; Department of Health, 1994 [IV]). There is no advantage in early weaning, which tends to be associated with the introduction of low energy foods such as pureed rice, fruits and vegetables. Milk products are a major component of the diet during the first year of life and it is recommended to continue breast milk or an artificial formula for at least the first 12 months. Fat-soluble vitamin supplements are also necessary (see *Section 5 - Vitamins*). The introduction of solids and cows' milk may require an increase in pancreatin therapy.

### 3.8.2 Pancreatin for older infants and young children

The smallest dose of pancreatin to control steatorrhoea and achieve a normal pattern of growth and weight gain should be used (Littlewood & Wolfe, 2000 [IV]).

The current Committee on Safety of Medicines (CSM, 1995 [IV]) recommendation is that *"Pancrease HL, Nutrizym 22 will no longer be indicated for children aged 15 years and under with cystic fibrosis, and it would be prudent for patients with cystic fibrosis not to exceed a daily dose of enzymes equivalent to 10,000 IU lipase/kg/day, regardless of which preparation is used".*

Patients with CF vary in their degree of pancreatic insufficiency and so their enzyme requirements will differ. It should be noted that pancreatin is prepared from animal sources, thus dosages are approximate. Moreover, the stated capsule dose is a minimum as capsules are overfilled to compensate for enzyme degradation during storage. The actual doses may exceed the stated minimum dose by 20-50% (O'Hare et al, 1995 [IIb]).

On average, infants and young children require higher doses of pancreatin/kg body weight than older children and adults. This reflects their higher fat intake (5 g fat/kg/day compared with the average adult intake of 2 g fat/kg/day). Traditionally, enzymes have been prescribed on the basis of one dose for meals and a smaller dose for snacks. Better control of enzyme dose can be achieved by titrating dose against the fat content of the meal so that a low fat main meal such as breakfast may require fewer enzyme capsules than a fatty snack such as chocolate or potato crisps (Beckles Willson et al, 1998 [IIb]). On this basis, most patients require 50-100 IU lipase/g dietary fat/kg/day (Durie et al, 1998 [IIb]).

## 3.9 Pre-school years

Dietary counselling and advice are essential during this period when long-term feeding habits are developing (Ramsey et al, 1992 [IV]). Behavioural feeding problems are common in children of this age, as the child begins to assert its individuality. The pressure to maintain growth rates in children, together with toddler food fads, can often be a source of parental anxiety. Early intervention by members of the multi-disciplinary team at the Specialist CF Centre (particularly the dietitian and psychologist) to identify problems and advise and support parents and carers over this period can help minimise these issues and avoid the development of long-term behavioural feeding problems

(MacDonald 1996 [IV]; Stark et al, 1997 [III]; Simmons et al 1995 [III]). The booklets *Nutrition in Cystic Fibrosis - A Guide for Children and Parents* (CF Trust) and the leaflet *Help, My Child Won't Eat* (Paediatric Group of the British Dietetic Association) are useful to provide practical support strategies. The expert involvement of a family psychologist is necessary if behavioural problems have become entrenched.

### 3.10 Adolescents and adults

The goal of nutritional management in older people with CF is to maintain or restore a normal nutritional status and normal growth. The increased energy requirements are best achieved orally and the main role of the CF dietitian is to encourage a varied, high energy intake, with supplements as necessary.

Adolescence is a period of transition between childhood and adulthood. It is a time of change. The main growth spurt occurs during adolescence although the timing will vary between gender and individuals. Adolescence is also the time when sexual development occurs though in some individuals with CF and particularly those with poor nutrition this may be delayed. Requirements for nutrients such as protein and energy will be at their highest during the period of peak growth. In addition, a good calcium intake is essential to maximise bone density. Poor nutrition at this time can result in a lower peak bone mass. The nutritional goal at this time is to maximise growth potential.

Teenagers have a desire to become independent. They are likely to experiment, push boundaries, reject rules and authority and take risks. Food choice is one likely target for testing this independence. Snacking or "grazing" is a common pattern of eating with most adolescents rather than the traditional three meals per day. Parents may feel their teenager exists solely on junk food and snacks. This is perfectly normal and it is not necessarily undesirable since increased eating frequency is a useful way of meeting high-energy requirements.

Denial, treatment rejection and poor adherence to enzyme, vitamin and nutritional supplementation are common. Compromise is essential to minimise the consequences to both nutritional status and health, of this rebellious time whilst encouraging increasing independence. Despite the continuous emphasis on dietary intake, enzyme supplementation and weight gain adolescents and young adults with CF show eating behaviour and body image perceptions similar to their healthy peers (Abbott et al, 2000 [III]).

### 3.11 Recommendations

- ***Individual assessment of nutritional needs should be reviewed regularly by a dietitian experienced in CF and modified, according to the changing clinical and psychosocial needs of the patient [B].***
- ***Breast milk or whey-based artificial formulae are recommended from birth [B].***
- ***Infants require unrestricted feed volumes to achieve optimum growth; demand feeding is appropriate for both breast and bottle methods [B].***
- ***Poor growth or surgery for meconium ileus may require the use of nutritional supplements or a hydrolysed infant formula. Energy supplementation may be necessary if an infant is failing to thrive [B].***
- ***Sodium supplementation may be required in hot environments [B].***
- ***Introduction of solids should commence at 4-6 months of age; early weaning is not recommended [C].***

- *Microsphere or mini-microsphere pancreatic enzyme preparations should be used and are well tolerated in infants. Pancreatin dosage should be individually titrated with dietary intake and conform with the 1995 CSM recommendations [B].*
- *Children should be encouraged to swallow whole enzyme capsules at the earliest opportunity [C].*

## 3.12 Appendix - Pancreatin preparations available in the UK

| Standard strength | High strength |
|---|---|
| Creon 10,000† | Creon 25,000† |
| Nutrizym GR* | Nutrizym 22* |
| Nutrizym 10* | Pancrease HL * |
| Pancrease† | |
| Pancrex‡ | |
| Pancrex V‡ | |

*†Microsphere and microtablet pancreatic enzyme preparations containing porcine pancreatin coated with a thin layer of acid resisting phthylate.*

**Eudragit L30 D55 coated pancreatic enzyme preparations.*

*‡Non microsphere preparations.*

*Microtablets contain pellets of similar sizes.*
*Microspheres contain pellets of different sizes.*

## 3.13 Appendix - Minimum enzyme content (BP Units) of pancreatin preparations

| Name | Maker | Lipase | Protease | Amylase |
|---|---|---|---|---|
| **Enteric-coated microspheres** | | | | |
| **Nutrizym GR** | Merck | 10,000 | 650 | 10,000 |
| **Pancrease** | Janssen Cilag | 5,000 | 330 | 2,900 |
| **Enteric coated minimicrospheres** | | | | |
| **Creon 10000** | Solvay | 10,000 | 600 | 8,000 |
| **Creon 25000** | Solvay | 25,000 | 1000 | 18,000 |
| **Enteric-coated microtablets** | | | | |
| **Nutrizym 22** | Merck | 22,000 | 1,100 | 19,800 |
| **Nutrizym 10** | Merck | 10,000 | 500 | 9,000 |
| **Pancrease HL** | Janssen Cilag | 25,000 | 1250 | 22,500 |
| **Cotazym S** | Organon | 8000 | 30,000 | 30,000 |

**Other enzyme preparations available in the UK overleaf**

### Other enzyme preparations available in the UK

| Name | Maker | Lipase | Protease | Amylase |
|---|---|---|---|---|
| **Pancrex V Forte Tablets** *Enteric coated tablets* | Paine & Byrne | 5,600 | 330 | 5000 |
| **Pancrex V Tablets** *Enteric coated tablets* | Paine & Byrne | 1900 | 110 | 1700 |
| **Pancrex V capsules** *Capsules* | Paine & Byrne | 8000 | 430 | 9000 |
| **Pancrex V capsules '125'** *Clear capsules* | Payne & Byrne | 2950 | 160 | 3300 |
| **Pancrex V Powder** *Buff powder* | Paine & Byrne | 25000 | 1400 | 30000 |
| **Pancrex granules** *Coated granules* | Paine & Byrne | 5000 | 300 | 4000 |

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# 4. NUTRITION AND PREGNANCY

## 4.1 Nutritional influences on pregnancy outcome

**4.1.1** Women with cystic fibrosis can have a successful pregnancy without compromising long-term nutritional or pulmonary function (Olsen, 1997 [IV]). However, there is little research evidence upon which to base recommendations for management. In general published studies report improved pregnancy outcomes in women who are well nourished and have less severe pulmonary dysfunction, provided optimal medical and obstetric care is given (Canny, 1993 [IV]). Patients who have diabetes should be referred to a specialist diabetologist, as blood sugar control should be optimal throughout pregnancy.

**4.1.2** Outcomes have improved over the past two decades, with accumulating clinical experience demonstrating an association with better pulmonary function prior to pregnancy (FEV1 and FVC >50%), maintenance of lung function during pregnancy (Kent & Farquharson, 1993 [IV]) and a weight gain of at least 10 kg throughout pregnancy (Cohen et al, 1980 [IV]; Geddes, 1992 [IV]). Other positive factors for outcome include appropriate weight for height at conception (BMI 19 to 25), the length of gestation, presence of pancreatic sufficiency and a team approach to medical and obstetric care including dietitian, physiotherapist, CF nurse, social worker and psychologist (Olsen, 1997 [IV]; Canny, 1993 [IV]; Edenborough et al, 1995 [IV]; Edenborough, 2001 [IV]).

**4.1.3** Rapid deterioration in clinical status, particularly lung function, correlates more strongly with poor outcome, for mother and infant, than severe pre-existing impairment. The higher incidence of pre-term delivery of infants born to women with CF largely explains the increased perinatal death rates. Poor maternal nutrition and pregnancy weight gain, together with chronic hypoxia may be contributing factors (Olsen, 1997 [IV]).

## 4.2 Preconceptional assessment

A preconceptional nutritional assessment at the Specialist CF Centre can help identify the strengths and weaknesses of an individual's nutritional status prior to conception and offer an early chance to optimise care. A review of women with CF showed over 50% of pregnancies to be planned (Morton, 1995 [III]). When the pregnancy is unplanned, counselling will be needed at the earliest opportunity. This can be an opportunity to explain the increased risk (2.5%) of having a child with CF and the certainty of its carrier status. Genetic counselling and screening should also be offered. The availability and risks associated with chorionic villus sampling should be discussed. Women should be made aware of the increased risks of foetal growth retardation, gestational diabetes and pre-term labour and delivery (Canny, 1993 [IV]).

A full nutritional assessment is required and should include the following:

- Weight and height.
- Body mass index - weight [kg]/height $[m]^2$.
- Diet history, including a full computerised assessment of dietary intake.
- Review of pancreatin therapy; appropriate dose necessary to minimise malabsorption and control gastrointestinal symptoms.
- Measurement of plasma vitamin A, D, and E to establish levels are within the normal range and review compliance (see *Section 5 - Vitamins* for details and cautions).
- Assess iron and folate status to correct any deficiencies.
- Advice on folic acid supplementation - 400 mcg daily until the $12^{th}$ week of pregnancy (Department of Health, 1992 [III])
- Review diabetic status and optimise control, as appropriate (see *Section 7.3 - CF related diabetes mellitus*).
- Discussion of food safety issues (listeria/salmonella; as for all pregnant women).

## 4.3 Weight gain during pregnancy

In normal pregnancy weight gain varies widely, with 12.5 kg being the average reported total (Hytten & Chamberlain, 1991 [III]). In CF, pregnancy weight gain has been reported as significantly less than that of healthy women (Edenborough et al, 1995 [III]). An increase in weight of at least 10 kg, throughout pregnancy, has been associated with a good outcome (Cohen, 1980 [IV]; Geddes, 1992 [IV]). Weight gain may be compromised by periods of poor appetite during chest exacerbations and hospital admissions, or if lung function deteriorates during pregnancy (Olsen, 1997 [IV]). Clearly women with CF require additional nutritional support during pregnancy and their weight should be monitored at frequent hospital visits, perhaps as often as every 4 - 6 weeks. The ideal recommended weight gain might not be achievable in many patients, especially those with poorly controlled malabsorption or severe chronic pulmonary disease. Nutritional supplementation may be necessary, either orally or enterally (Hilman & Aitken, 1996 [III]), (see *Section 6. - Invasive nutritional support*).

The energy cost of pregnancy is 70,000 kcals and is largely achieved by reduced energy expenditure. Studies of healthy women have only shown an increased calorie intake in the last few weeks of pregnancy. Therefore, dietary reference values recommend a daily increase in energy intake of 200 kcal throughout the last trimester (Department of Health, 1991 [IV]). Also during this period, the enlarged uterus causes increased intra-abdominal pressure resulting in shortness of breath and further compromising lung function. Gastro-oesophageal reflux and constipation may be experienced. Patients will need specific and practical advice from an experienced CF dietitian on how to overcome these symptoms, including eating small, frequent meals with fluids in between.

## 4.4 Vitamin status

For advice, see 5.2.4 in *Section 5 - Vitamins.*

## 4.5 Lactation

As with all pregnancies the mother's preferred infant feeding method should be respected. Taking into account her CF condition, this should be discussed at the earliest opportunity in the pregnancy with each woman, and between the Specialist CF Centre and midwifery team. There is no contraindication to a mother with CF breastfeeding, provided an adequate energy intake can be maintained. Breastfeeding has an energy cost for the mother, which will need to be met by an increased intake of 500 kcal per day (Department of Health, 1991 [IV]). In practice appetite increase, rather than use of supplements, may be sufficient.

Once lactation has been established breast milk has been shown to have a normal sodium content (Kent & Farquharson, 1993 [IIb]). A good understanding of the basic principles of lactation (supply and demand) together with adequate support for the breastfeeding mother are required for success (Raj & Plichta, 1998 [IV]). Complications resulting from the delivery, including the need for additional physiotherapy, intravenous antibiotics, Caesarean section or pneumothorax, may make establishing lactation difficult. Breastfeeding is time consuming and the mother will need to consider how she will cope with this alongside her own medical treatments. A supportive partner and/or family are a great advantage.

## 4.6 Antibiotic therapy and lactation

Pregnancy alters the pharmacokinetics of many drugs and certain antibiotics are contraindicated during pregnancy and lactation. However, because antibiotic policies vary across the country and drug data sheets are altered frequently, appropriate medications should be reviewed and checked with the hospital pharmacist, on a patient specific basis (Briggs et al, 1997 [IV]). Further details can be found in *Section 6.9.4 of Antibiotic Treatment for Cystic Fibrosis. Report of the UK CF Trust's Antibiotic Group. London, Cystic Fibrosis Trust, 2000 [IV].*

## 4.7 Recommendations

- ***Close liaison between the Specialist CF Centre staff and obstetric team to ensure effective and consistent management of both CF and the pregnancy [C].***
- ***Preconceptional and early pregnancy nutritional counselling and a full nutritional assessment [C].***
- ***Correction of nutritional deficiencies particularly iron and folic acid [C].***
- ***Frequent visits to the Specialist CF Centre, perhaps 4 - 6 weekly [C].***
- ***Aim to achieve a weight gain of at least 10 kg during the pregnancy (0.5 kg/week from 20 weeks gestation) [C].***
- ***Women with CF may breastfeed their infants provided they can maintain an adequate energy intake [C].***
- ***Aggressive management of acute pulmonary exacerbations [C].***
- ***Review antibiotic therapy during pregnancy and lactation [C].***
- ***Folic acid supplementation in the preconceptional period and throughout the first trimester [A].***

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# 5. VITAMINS

## 5.1 Introduction

Malabsorption of fat-soluble vitamins is likely in most patients with cystic fibrosis, particularly those who are pancreatic insufficient (Congden et al, 1981 [IIb]; Ramsey et al, 1992 [IV]). Biochemical evidence of fat-soluble vitamin deficiency has been found by two months of age in untreated screened infants with cystic fibrosis (Sokol et al, 1989 [IIb]). Low vitamin levels are associated with poorer clinical status (Rayner et al, 1989 [III]), and reduced lung function (Carr & Dinwiddie, 1996 [III]). Whether this is related to the role of vitamin A in the immune system or its antioxidant properties is unclear.

Since the introduction of improved pancreatic enzymes, normal to high fat diets and routine vitamin supplementation, clinical evidence of fat-soluble vitamin deficiency is rarely seen. The evidence suggests that with modern therapy only supplements of vitamin A, D and E are required in uncomplicated cystic fibrosis (Peters & Rolles, 1993 [IV]). Those patients with poorly controlled malabsorption, liver disease, late diagnosis, bowel resection and those who adhere poorly to therapy will remain at risk of developing clinical or subclinical deficiencies of fat-soluble vitamins (Sokol et al, 1989 [IIb]; Rayner et al, 1989 [IIb]; Peters & Rolles, 1993 [IV]; Bye et al, 1985 [IV]).

## 5.2 Vitamin A (1 µg=3.3 IU)

Vitamin A can be obtained in two forms: as preformed vitamin A (retinol/retinol esters) or from some of the carotenoid pigments, mainly β-carotene, that can be cleaved in the body to give retinol. Over one hundred carotenoid pigments have been found but only a few have structures that enable them to act as a precursor of vitamin A. It is thought they may be more important as antioxidants (Burton, 1989 [IV]; Winklhofer-Roob et al, 1994 [III]; Winklhofer-Roob, 1995 [III]; Renner et al, 2001 [IIa]).

Vitamin A deficiency was described in one of the early reports of cystic fibrosis (Andersen, 1939 [III]). Today, clinical evidence of vitamin A deficiency is rarely seen. However plasma levels of vitamin A are lower in both pancreatic sufficient and pancreatic insufficient patients than healthy controls (Congden et al, 1981 [IIb]; Underwood & Denning, 1972 [IIb]; Lancellotti et al, 1996 [IIb]). Impaired dark adaptation associated with poor nocturnal vision has been reported in well-nourished patients receiving vitamin A supplementation and concurrent pancreatic enzyme replacement therapy (Huet et al, 1997 [IIb]).

Vitamin A deficiency in CF may be multifactorial and not simply a consequence of malabsorption (Kawchak et al, 1999 [IIb]). There is an increased faecal loss of retinol in CF unrelated to the degree of fat in the stool (Ahmed et al, 1990 [IIb]) suggesting a possible defect in the handling of retinol by the gastrointestinal tract. Earlier work describes reduced mobilisation from liver stores (Underwood & Denning, 1972 [III]), low plasma levels of retinol binding protein (Rees Smith et al, 1972 [III]) and deficiency of the essential co-factor zinc (Palin et al, 1979 [III]) as contributing factors.

### 5.2.1 Assessment of vitamin A status

Plasma retinol concentrations are insensitive indicators of vitamin A status. Vitamin A may accumulate in the liver (Eid et al, 1990 [III]), but liver stores cannot be accurately assessed in living subjects. The plasma level of vitamin A usually correlates with the level of retinol binding protein (Rasmussen et al, 1986 [IIb]). Thus, low plasma vitamin A levels may reflect low retinol binding

protein output by the liver rather than vitamin A deficiency. Plasma retinol concentrations may also be depressed in acute infection (Duggan et al, 1996 [III]); therefore, plasma vitamin A levels should be checked at a time of clinical stability. Assessment of stool losses (of retinol) may provide useful information but is not routinely used in clinical practice (Ahmed et al, 1990 [IIb]).

### 5.2.2 Vitamin A toxicity

Hypervitaminosis A has been reported in an infant with CF following a loading dose of vitamin A. Postmortem analysis of liver tissue has shown levels 3.5 times that of normal in some people with cystic fibrosis (Eid et al, 1990 [III]).

### 5.2.3 Vitamin A recommended dose

The recommended dose for vitamin A has not been adequately established.
A range of doses from 5,000 to 10,000 IU per day depending on age has been recommended (Peters & Rolles, 1993 [IV]).

### 5.2.4 Special considerations

**Pregnancy**
Retinol is teratogenic. A relationship has been suggested between the incidence of birth defects in infants and high vitamin A intakes (10,000 IU or 3000 mcg/day) during pregnancy (Rothman et al, 1995 [III]). As a precautionary measure women in the UK who are or might become pregnant have been advised not to take supplements containing vitamin A unless advised to do so by a doctor (Chief Medical Officer, 1990 [IV]). Current practice varies between Specialist CF Centres. In women with CF serum vitamin A levels should be checked at the start of pregnancy. If plasma levels were high it would appear prudent to reduce the level of vitamin A supplementation. If levels are low or normal it would be reasonable to continue vitamin A supplementation at a level less than 10,000 IU daily.

## 5.3 Vitamin D (1 µg=40 IU)

The two main forms of vitamin D are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Cholecalciferol is derived from ultraviolet (UV) irradiation on 7-dehydrocholesterol in the skin. For most people in the UK UV irradiation can provide more than 80% of the normal requirement.

### 5.3.1 Vitamin D deficiency

Clinical evidence of vitamin D deficiency is rare in cystic fibrosis. Reduced plasma levels of 25-hydroxyvitamin D have been described in some studies (Congden et al, 1981 [IIb]; Sokol, 1989 [IIb]; Durie & Pencharz, 1989 [III]), and osteopoenia and osteoporosis have been recognised in both children and adults with CF (Bachrach et al, 1994 [III]; Bhudhikanok et al, 1996 [III]; Haworth et al, 1999 [IIb]). Early studies in patients with CF suggested reduced cortical thickness of the appendicular skeleton (Hahn et al, 1979 [III]) and subsequent studies using DEXA showed reduced composite cortical and trabecular bone mineral density (BMD) of the axial skeleton in adolescents and adults with cystic fibrosis (Grey et al, 1993 [IIb]). However, initial studies with DEXA failed to allow for the confounding effects of small bone size, which leads to an underestimate of BMD (Carter et al, 1992 [III]). Thus, it is difficult to determine whether reduced BMD in these studies was a genuine reduction. Salamoni et al, compared BMD of patients with CF with size-matched controls and found no reduction in BMD in well-nourished children with cystic

fibrosis (Salamoni et al, 1996 [IIb]). Nevertheless, increased skeletal fragility has been widely reported in adolescent and adult patients with CF (Baroncelli et al, 1997 [III]) but this cannot be fully accounted for by reduced BMD, therefore a more detailed assessment of bone size and structure is required.

The aetiology of reduced bone mineralisation in patients with CF is probably multifactorial and appears to correlate with poor nutritional status and overall Shwachman clinical score. Other factors including chronic lung infection, vitamin D deficiency, calcium intake, corticosteroid use and limited exercise capacity may also be important.

### 5.3.2 Assessment of status

Plasma 25-hydroxyvitamin D gives a good indication of vitamin D status; however, seasonal variations in plasma vitamin D levels are well recognised (Reiter et al, 1985 [III]); Rayner, 1992 [III]; Wolfe et al, 2001 [IIb]). Recent work suggests that vitamin D levels should be maintained towards the upper end of the normal range throughout the year (Elkin et al, 2001 [IIb]).

### 5.3.3 Toxicity

Vitamin D toxicity has not been reported in cystic fibrosis.

### 5.3.4 Vitamin D recommended dose

A range of dose recommendations can be found (Peters & Rolles, 1993 [IV]; Leonard and Knox, 1997 [III]). In most studies doses of 400 to 800 IU have achieved low normal serum levels (Peters & Rolles, 1993 [IV]). However, it is now believed that vitamin D levels should be maintained towards the upper end of the normal range. Doses exceeding 800 IU will be required in some patients. Dose should be guided by plasma levels and titrated accordingly.

### 5.3.5 Vitamin D special considerations

Vitamin D requirements are increased in pregnancy and lactation. Supplementary vitamin D to achieve an intake of 400 IU (10 mcg)/day is recommended for all women during pregnancy and lactation (Department of Health, 1991 [IV]). Additional supplementation of 400 to 800 IU (10-20 mcg) may be required in women with CF during pregnancy.

## 5.4 Vitamin E (1 mg=1.5 IU)

Vitamin E (alpha-tocopherol) accounts for 90% of vitamin E present in human tissues. The tocotrienols are less potent. Vitamin E is an antioxidant and protects cell membranes from free radical oxidative damage (McKay et al, 1972 [IV]). Vitamin E may be important in controlling the progression of lung disease in CF because of this antioxidant role.

### 5.4.1 Deficiency of vitamin E

Plasma levels of vitamin E fall in infants with CF during the first weeks of life and this deficiency can remain in a minority of patients despite supplementation (Sokol et al, 1989 [III]). Haemolytic anaemia has been reported in infants with CF and shortened erythrocyte survival time has been described (Farrell et al, 1977 [III]). Nerve conduction studies may demonstrate increased sural nerve conduction/latency and decreased action potential amplitude (Cynamon et al, 1988 [IIb]).

Visual and somatosensory evoked potentials may also be abnormal (Sitrin et al, 1987 [IIb]; Kaplan et al, 1988 [IIb]). At post-mortem there is degeneration of the posterior columns, loss of large unmyelinated axons in peripheral nerves and retinal degeneration.

### 5.4.2 Assessment of vitamin E status

Serum or plasma vitamin E levels represent only a small proportion of total body vitamin E (McKay et al, 1972 [IIb]) and may not accurately reflect vitamin E status. Levels in serum will also vary according to levels of carrier lipoprotein so vitamin E/fasting lipid ratio should be determined. Erythrocyte vitamin E levels correlate with the dose of the oral vitamin E supplement (Peters & Kelly, 1996 [IV]).

### 5.4.3 Toxicity

A safe upper level for supplementation has not been determined although large doses appear to be tolerated without adverse effects.

### 5.4.4 Dose of vitamin E

Erythrocyte vitamin E was found to normalise in most children with CF when they were supplemented with 100 mg vitamin E daily (Peters & Kelly, 1996 [IV]). Dose recommendations of 10 to 200 mg can be found, dependent on age (Peters & Kelly, 1993 [IV]; Leonard and Knox, 1997 [III]).

Recent studies have suggested that people with CF have inadequate antioxidant defences to cope with elevated oxidative stress, which they regularly experience (Brown et al, 1996 [III]); it has been suggested that current doses of vitamin E may be too low (Winklhofer-Roob et al, 1996 [III]).

## 5.5 Vitamin K

Although vitamin K deficiency has been considered to be rare in CF, patients are at increased risk of developing vitamin K deficiency due to fat malabsorption, bile salt deficiency, liver disease and antibiotic therapy (Durie & Pencharz, 1989 [III]; Durie, 1994 [IIb]).

Subclinical vitamin K deficiency, as shown by elevated protein induced in vitamin K absence (PIVKA II levels) is almost universal in pancreatic insufficient children with cystic fibrosis (Rashid et al, 1999 [IIb]).

Vitamin K is required for the formation of osteocalcin, which is involved in bone metabolism. Sub-clinical deficiency may play a role in osteopenia and osteoporosis in patients with cystic fibrosis.

### 5.5.1 Assessment of vitamin K status

Plasma vitamin K levels are unreliable for assessment of status (Durie, 1994 [IIb]; Rashid et al, 1999 [IIb]). Functional measures of vitamin K status are preferred but undercarboxylated osteocalcin and PIVKA-II measurements are not routinely available in the United Kingdom. Prothrombin levels are indicative of a severe vitamin K deficiency, but are rarely abnormal even in advanced CF liver disease (Durie, 1994 [IIb] Rashid et al, 1999 [IIb]). However, it has been suggested that prothrombin time and coagulation/clotting studies should be carried out on all patients with CF before any surgical procedure (Littlewood, 1989 [IV]).

Subclinical vitamin K deficiency has been demonstrated in 24 patients with CF (3 to 38 years), compared to 51 normals using assays for factor II coagulant activity (CA) and factor II antigen (CA to antigen ratio 0.77; N = 0.85-1.0) (Corrigan et al, 1981 [IIa]). Using PIVKA II levels subclinical vitamin K deficiency has been demonstrated in 78% of pancreatic insufficient patients not receiving vitamin K supplements, compared with 100% of patients with CF liver disease and 33% of pancreatic sufficient patients (Rashid et al, 1999 [IIb]). Supplementation with vitamin K reduces the incidence of abnormal PIVKA II levels (Beker et al, 1997 [IIb]; Wilson et al, 1997 [IIb]).

### 5.5.2 Vitamin K toxicity

Has not been reported in cystic fibrosis.

### 5.5.3 Vitamin K recommended dose

A recommended dose for vitamin K in CF is not established. A dose of 5 mg vitamin K1 given weekly did not correct subclinical vitamin K deficiency (Beker et al, 1997 [III]). A smaller daily dose (mean of 0.18 mg) was more effective in returning a percentage of patients with subclinical vitamin K deficiency to normal (Wilson et al, 1997 [IIb]; Wilson et al, 2001 [IIb]). However the dose was insufficient to normalise PIVKA II levels in all patients. As the metabolic turnover time for vitamin K is approximately once every 24 hours (Olsen, 1994 [III]), a daily rather than weekly dose of vitamin K may be important in cystic fibrosis. Further work is needed to obtain a recommended dose for vitamin K supplementation.

## 5.6 Water-soluble vitamins

Water-soluble vitamins appear to be well absorbed. Routine supplementation of water-soluble vitamins is unnecessary (Congden et al, 1981 [IIb]; Peters & Rolles, 1993 [IV]) unless there is documented evidence of poor dietary intake. Parental vitamin $B_{12}$ may be required for the patient who has had extensive surgery for meconium Ileus (Collins et al, 1984 [IIb]).

Vitamin C and β-carotene are currently receiving attention due to their antioxidant properties (Winklhofer-Roob et al, 1997 [III]; Rust et al, 1998 [IIb]; Range et al, 1999 [IIb]; Benabdeslam et al, 1999 [III]; Madrassi et al, 2000 [IIb]; Wood et al, 2001 [III]).

## 5.7 When should vitamin supplements be started?

Vitamin A, D and E supplements should be commenced on diagnosis in pancreatic insufficient patients. Pancreatic sufficient patients should have their serum levels monitored annually and supplementation should be commenced when low levels are detected. Vitamin K should be commenced if there is evidence of liver disease or a prolonged prothrombin time.

## 5.8 When should patients take their vitamins?

In pancreatic insufficiency pancreatic enzyme replacement therapy (PERT) may enhance absorption of the fat-soluble vitamins. It would appear logical for vitamin supplements to be taken at meal times with pancreatic enzymes.

## 5.9 Assessing and monitoring status

As previously described for individual vitamins. Laboratory techniques make it possible to measure plasma vitamin levels, though this will not necessarily accurately reflect vitamin status. Monitoring of fat-soluble vitamin status should be carried out as part of the Annual Review of patients with cystic fibrosis. Experience suggests that the effects of alterations in therapy should be checked after 3 to 6 months.

## 5.10 General recommendations for vitamin supplementation

- *Supplemental vitamin A, D and E should be commenced on diagnosis in pancreatic insufficient patients with cystic fibrosis [B].*
- *Plasma fat-soluble vitamin levels should be measured as part of the Annual Review and the supplement dose adjusted according to plasma levels [B].*
- *Pancreatic sufficient patients should also be monitored by measuring serum levels annually. Supplemental vitamin A, D, E should be commenced when low levels are detected [B].*

**Vitamin A recommendations:**

- *Retinol binding protein and plasma zinc may aid interpretation of low plasma levels although are not required for all patients [B].*
- *Dose:*
  - *< 1 year : 4,000 IU (1,200 mcg) daily*
  - *> 1 year: 4,000 to 10,000 IU (1,200 to 3,000 mcg) daily [B].*

**Vitamin D recommendations:**

- *There should be awareness of seasonal variations in levels [B].*
- *Dose:*
  - *Infants: 400 IU (10 mcg) daily*
  - *Children: 400 to 800 IU (10 to 20 mcg) daily*
  - *Adults: 800 to 2,000 IU (20 to 50 mcg) daily [B].*

**Vitamin E recommendations:**

- *Plasma vitamin E/lipid ratio is essential for the accurate interpretation of low vitamin E levels [B].*
- *Dose:*
  - *Birth to 1 year: 10 to 50 mg daily*
  - *1 year to 10 years: 50 to 100 mg daily*
  - *10 years: 100 to 200 mg daily [B].*

**Vitamin K recommendations:**

- *Assessment by prothrombin levels (although levels do not correlate well with plasma vitamin K levels) [C].*
- *Factor II coagulant activity / factor II antigen ratio (normal 0.85 to 1.0) is useful [C].*
- *Monitor prothrombin levels as an indicator of vitamin K status at Annual Review if liver disease is present or suspected or following intestinal resection [C].*
- *Recommended dose is not established; suggested children and adults receive vitamin K 10 mg daily [C].*

## 5.11 Table - Vitamin content of commonly used supplements

| Preparation | A (IU) | D (IU) | E (mg) | C (mg) | K (mg) |
|---|---|---|---|---|---|
| Abidec 0.6 ml | 4,000 | 400 | Nil | 50 | Nil |
| A+D caps/capsule | 4,000 | 400 | Nil | Nil | Nil |
| Halibut liver oil caps/capsule | 4,000 | Variable | Nil | Nil | Nil |
| Halycitrol emulsion units (5 ml) | 4,600 | 380 | Nil | Nil | Nil |
| Vitamin caps BPD/capsule | 2,500 | 300 | Nil | Nil | Nil |
| Dalivit drops (0.6 ml) | 5,000 | 400 | Nil | 50 | Nil |
| Forceval caps/capsule | 2,500 | 400 | 10 | 60 | Nil |
| Forceval Junior/capsule | 1,250 | 200 | 5 | 25 | Nil |
| Ketovite tabs/tablet | Nil | Nil | 5 | 16.6 | Nil |
| Ketovite liquid/5 ml | 2,500 | 400 | Nil | Nil | Nil |
| Vitamin E susp/ml | Nil | Nil | 100 | Nil | Nil |
| Vitamin E tabs/tablet | Nil | Nil | 50/200 | Nil | Nil |
| Konakion/tablet | Nil | Nil | Nil | Nil | 10 |
| Menadiol phosphate/tablet | Nil | Nil | Nil | Nil | 10 |

## 5.12 Table - Summary of vitamin supplement doses

| Age | Vitamin A | Vitamin D | Vitamin E |
|---|---|---|---|
| < 1 Year | 4,000 IU (1,200 µg) | 400 IU (10 µg) | 10 - 50 mg |
| > 1 Year | 4,000 - 10,000 IU (1,200 - 3,000 µg) | 400 - 800 IU (10 µg - 20 µg) | 50 - 100 mg |
| Adults | 4,000 - 10,000 IU (1,200 - 3,000 µg) | 800 - 2,000 IU (20 - 50 µg) | 100 - 200 mg |

*Doses should be guided by serum levels.*

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# 6. INVASIVE NUTRITIONAL SUPPORT

## 6.1 Introduction

Nutritional support should be an integral part of overall care and requires close clinical evaluation. It is stressed that any intervention should be in keeping with local policies and guidelines. When advanced lung disease supervenes, energy expenditure rises and energy imbalance may result. The increased energy requirements in cystic fibrosis have been estimated to be approximately 120-150 percent of the required nutrient intakes for age (Vaisman et al, 1987 [IIb]). The increase in energy expenditure is related to chronic lung disease, continuous inflammation, acute exacerbation of infection and metabolic derangement. Reduced intake may be a result of anorexia, vomiting, gastro-intestinal complications, distal intestinal obstruction syndrome, depression, behavioural problems and iatrogenic dietary restrictions in energy resulting from the recommendation of a low fat diet.

Nutritional failure in CF is multifactorial and management includes optimising oral intake, reviewing the adequacy of enzyme therapy, treatment of the chest, and exclusion of CF related diabetes mellitus before embarking upon invasive nutritional support.

## 6.2 Use of oral supplements

If weight gain or growth is poor despite maximising the energy intake from the normal diet, the use of oral nutritional supplements may be beneficial. There are a wide variety of these preparations available including energy only supplements, calorie and protein supplements and nutritionally complete supplements (see *Section 6.15 Nutritional supplements*). The type and quantity of supplement prescribed should be assessed on an individual basis. The choice is usually dependent on the patient's age, preference and nutritional requirements. Dietary supplements should complement the normal food intake; they should not replace food. It is best to take them either after a meal or as an in between meal snack so that they do not replace the appetite for normal food.

## 6.3 When to initiate enteral tube feeding *(see Section 2.6 Criteria for different stages of nutritional intervention)*

If after the use of oral nutritional supplements:
**In children -**

- a weight for height of <85%
- weight falling two centile positions
- no weight gain for 6 months.

**In adults -**

- BMI less than 19
- more than 5% weight loss over more than 2 months
- failure to gain weight during pregnancy.

## 6.4 Period of feeding

Several studies have shown supplemental feeding results in positive changes in body composition and growth velocity and increases the patient's ability to participate in activities of daily living (Levy et al, 1985 [III]). Other benefits of enteral feeding include improvements in body fat, lean body mass, muscle mass, height and improved muscle strength (Levy et al, 1986 [III]). Brief periods

of energy supplementation in chronically malnourished patients with CF have transient effects (Shepherd et al, 1986 [III]). It is evident that long-term approaches to artificial supplemental feeding may achieve and maintain normal nutrition in patients who are unable to meet their energy needs. To produce lasting benefit, many studies have shown enteral feeding should be continued long-term, to achieve significant improvement in catch up growth, lung function and positive changes in body composition (Boland et al, 1986 [III]; Steinkamp & von der Hardt, 1994 [III]).

The following guidelines are based on consensus of opinion due to lack of randomised controlled trials. Prior to decision-making, the patient and family should be informed about why feeding is important and how it will be of benefit, the different types of feeding available, delivery systems, how tubes are placed, frequency of feeding and arrangements for home feeding.

## 6.5 Enteral nutrition

The main routes of feeding are via nasogastric tubes (NG) or gastrostomies, which for most patients are sited percutaneously by endoscopic placement (PEG). Nasogastric tubes are advocated by some as a less permanent technique, which may reduce concerns over body image. Adolescent girls on enteral feeds improve their nutritional status, but not necessarily improve their self-image (Snarey et al, 1993 [III]).

### 6.5.1 Nasogastric feeding

Nasogastric feeding is simple and 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. Success depends on attitude with many patients preferring this route because of concerns over body image. Patients can easily be trained to pass the tubes themselves nightly to enable continuation of normal daily activities; others may keep the tube in-situ for weeks or months at a time. Nasogastric feeding may be preferable for patients with oesophageal or gastric varices, in whom gastrostomy placement may be unsuitable or high-risk. However, if nasogastric feeding is unsuccessful or not well tolerated, or long-term support is envisaged, gastrostomy insertion should be considered. Much depends on motivation. Most patients feed at night, others deliver several bolus feeds during the day. Patients should be encouraged to pass their own NG tube, although some will find insertion too difficult. Nasogastric tubes are rarely uncomfortable once in-situ and persisting discomfort suggests the tube is in the oesophagus or pharynx. The main disadvantages are coughing, which may displace the tube and swallowing enzymes with a tube in situ which can be a problem for some patients. Those with nasal polyps may find tube passage difficult.

### 6.5.2 Types of tubes

*Polyvinyl chloride (PVC) tubes:* These are used for short term enteral feeding and can be passed daily as they are cheap and can be replaced easily. If not replaced daily, tubes should be changed every week as the plasticizers leach out, causing the tube to stiffen. PVC tubes are less likely to be displaced than polyurethane tubes.

*Polyurethane and Silicone tubes.* These are designed for longer term nasogastric feeding and are much softer and more comfortable than PVC tubes. Each tube comes with its own guide-wire or style to allow it to be positioned. Manufacturers recommend that these tubes remain in place for a month before resiting. They can also be used for overnight feeding, removed during the day and re-passed as long as there is adherence to storage and cleaning instructions and local enteral feeding policy. Patients should be warned that tubes discolour with time.

### 6.5.3 Size of tubes

The use of tubes should conform to local hospital policy. Six French gauge paediatric incubator tubes and 8 French gauge fine bore feeding tubes are suitable for most feeds delivered by pump. Manufacturers advise maximum flow rates.

### 6.5.4 Complications of tube feeding *(see also A Pocket Guide to Clinical Nutrition from the Parenteral and Enteral Nutrition Group of the British Dietetic Association)*

| Complications | Suggestions for Prevention |
|---|---|
| Nasal discomfort | Use both nostrils.<br>Keep nostrils clean and dry. |
| Blocked tube | a) Flush with 20 ml warm water.<br>b) Flush with 20 ml of Cola drink.<br>c) Flush with 1/4 teasp. bicarbonate of soda in 20 mls water.<br>d) Flush with 1/4 teasp. pancreatic enzyme powder mixed with 20 mls water. |
| Aspiration | Feed in an upright position.<br>Check tube position before feeding.<br>Note: some feeds may be of low pH and produce errors on testing gastric aspirate. |
| Nausea/ bloating/vomiting | Manipulate rate/time of feeding.<br>Consider use of anti-emetic drugs and pro-kinetics such as erythromycin or domperidone.<br>Consider different type of feed. |

*Note: many of these problems also relate to gastrostomy feeding.*

## 6.6 Gastrostomy feeding

**6.6.1** Gastrostomy feeding is preferential for long-term nutritional support. Overnight feeding may be more comfortable via a gastrostomy, particularly during respiratory exacerbations. Additional bolus feeds can also be given during the day. Tubes are usually sited endoscopically under sedation although a general anaesthetic may be preferable for children. Operative placement may be considered in patients with a history of previous abdominal surgery. Pre-gastrostomy, if being placed under anaesthetic, patients should be admitted to treat any chest symptoms prior to anaesthesia. It is usual to stay for several days to learn the technique and for the home feeding system to be arranged. Patients have the option of a traditional gastrostomy 'G' tube or Button. As gastro-oesophageal reflux may be increased by gastrostomy placement, ambulatory pH measurements or contrast studies should be considered prior to performing the gastrostomy.

**6.6.2** Percutaneous gastrostomy tubes (PEGs) have a life-expectancy up to and beyond 2 years, after which time they can be replaced endoscopically. Newer style balloon buttons can be inserted into a ready-formed tract and changed by pulling out the existing PEG and simply inserting the button. No sedation or pain relief is usually necessary. It is usual to establish a tract by prior PEG

placement for up to 6 months before button insertion. However, recent papers suggest a button can be inserted as a primary procedure, which may reduce the potential morbidity of a second procedure in this high-risk group of patients. Two small studies (7 and 17 patients) showed no mortality and only minor morbidity (Griffiths, 1996 [III]) but concluded that more experience is needed before recommending placement as the initial procedure in infants and children (Treem et al, 1993 [III]).

### 6.6.3 Balloon button

These buttons have a limited lifespan in patients with CF, but ease of replacement counteracts this disadvantage. They are available in various sizes. The button balloon contains up to 10 mls water. If the balloon bursts the patient cannot aspirate any water; this indicates need for replacement. Enteral feeding is carried out in accordance with the hospital enteral feeding policy.

### 6.6.4 Complications of gastrostomy placement

Patients with CF may experience pain following insertion. This is perhaps due to their stronger abdominal muscles toned as a consequence of daily physiotherapy and coughing. In the first few days following PEG placement, pain relief may be required during physiotherapy.

An increased cough and fall in lung function may follow anaesthesia, prolonging hospital stay and necessitating intravenous antibiotics. Peritonitis is a more serious but relatively uncommon complication of PEG placement, the reported incidence being 1 - 8 % (Haws et al, 1966 [III]; Gauderer, 1991 [III]; Treem et al, 1993 [III]; Davidson et al, 1995 [III]; Corwin et al; 1996 [III]).

### 6.6.5 Care of gastrostomy tubes

Following placement of a gastrostomy, it is important to keep the site clean, dry and open to the air. The tube should be rotated as laid out in manufacturers' guidelines and flushed with water prior to and following each feed. Sticky PEG sites should be swabbed for bacterial and fungal culture and topical antimicrobial therapy prescribed. Antibiotic and steroid combinations (e.g Sofradex, containing dexamethasone, framycetin and gramicidin) may be effective where antibiotics alone have failed. The use of steroid aerosols (Budesonide MDI - 200 µg twice/day) sprayed around the PEG site may also improve difficult cases.

## 6.7 How to commence a feed

In the case of uncomplicated PEG placement, feeding usually is commenced within 24 hours or immediately following confirmation of correct nasogastric tube placement and gradually increased to reach the desired intake.

## 6.8 Types of feed

### 6.8.1 Examples of some available enteral formulae

| | POLYMERIC | ELEMENTAL/SEMI-ELEMENTAL |
|---|---|---|
| ADULT | | |
| | Ensure Plus | Emsogen |
| | Fresubin HP Energy | Nutrison Pepti |
| | Nutrison Energy | Peptamen |
| | Sondalis 1.5 | Perative |
| | Two Cal HN | |

| | POLYMERIC | ELEMENTAL/SEMI-ELEMENTAL |
|---|---|---|
| PAEDIATRIC | Fortini<br>Novasource Junior<br>Nutrini<br>Paediasure | MCT Pepdite/MCT Pepdite 1+<br>Pepdite/ Pepdite 1+ |

**A complete list of products can be seen in *Section 6.15 Nutritional Supplements.***

### 6.8.2 Elemental vs. polymeric feeds

Elemental feeds are generally lower in fat and contain a mixture of medium and long chain triglycerides, have high osmolality and lower calorie density. More concentrated feeds may be tolerated by some patients. Although there is little work comparing the efficacy of elemental vs. polymeric feeds, one study demonstrated steatorrhoea was no greater using polymeric formulae in combination with enzymes than an elemental feed (Kane et al, 1990 [IIb]).

## 6.9 Enzymes with feeding

There is insufficient evidence to advise whether pancreatic enzymes are necessary with elemental feeds. The following are guidelines based on a consensus opinion.

An initial dose based on the number of enzyme capsules taken for a main meal is advised with adjustment according to bowel symptoms and weight gain. Enzyme intake for polymeric feeds is dependent on rate of infusion and choice of feed i.e. calorie and fat content of feed. There is insufficient evidence as to the optimum time for enzymes to be taken with feeds. Patients are mainly advised half the dose pre-feed and the other half mid-feed or post-feed (depending upon whether they wake during the night) (Patchell et al, 1998 [III]). It is not routine practice to wake patients to take enzymes. Enzymes should be taken orally and not put down the tube. More trials are needed to confirm the optimum time for taking enzymes.

For mechanics of feeding (hanging time, bag changes etc.) refer to *A Pocket Guide to Clinical Nutrition from the Parenteral and Enteral Nutrition* Group of the British Dietetic Association or to local hospital policy.

## 6.10 Specialist feeds

High fat feeds such as Pulmocare (Abbott) have been advocated in CF for patients with severe lung disease as they result in less carbon dioxide production and lower the respiratory quotient. However, one study compared low, medium and high carbohydrate formula feeds and examined whether the increase in $VCO_2$ and ventilatory demands in carbohydrate loading could be detrimental to patients with moderate to severe lung disease. They concluded that despite the highest increase in carbon dioxide after a high carbohydrate formula, patients who were clinically stable were able to increase their minute volume sufficiently to prevent worsening hypoxia or carbon dioxide retention (Kane & Hobbs, 1991 [IIb]).

## 6.11 Timing of feeds

Timing of feeding is very important and should be adjusted to the patient's lifestyle. Feed times can be adjusted to reduce any risk of affecting daytime appetite. Monitoring for glucose intolerance is

also important; patients receiving supplemental feeds who demonstrate repeated blood sugars >11.1 mmol/l during the feed may benefit from the addition of insulin given before the feed. Domperidone can also be used to help reduce gastro-oesophageal reflux or early morning vomiting (Bines et al, 1992 [IIb]).

### 6.12 Nutritional management of ventilated patients

When patients with CF require ventilation, either due to a sudden deterioration in respiratory function or as a bridge to transplantation, feeding becomes a complex issue. Pancreatic enzyme supplements cannot be taken orally. The feed of choice is therefore an elemental formula. Feeds are better given continuously over 24 hours and enzymes may not be needed. If there is concern over malabsorption, administration of powdered pancreatic enzyme mixed with water may help to improve absorption and should be considered. The addition a proton pump antagonist or an $H_2$ blocker may also enhance pancreatin function. In the case of nasal ventilation, naso-gastric feeding can continue once an adequate seal has been established between the mask and face.

### 6.13 Parenteral nutrition

Parenteral nutrition (TPN) is an option for short-term maintenance of nutrition after surgery. Several studies have shown a clinical improvement in nutritional status (and lung function) with supplementary parenteral feeding (Shepherd et al, 1980 [III]; Mansell et al, 1984 [III]; Lester et al, 1986 [III]; Skeie et al, 1987 [III]). Shepherd et al administered parenteral nutrition providing 90-100% of recommended daily allowance and permitted oral food intake, providing over 130% of recommended daily allowance for 3 weeks. The study demonstrated weight gain and improved respiratory function at 6 months. However, the numbers were small and these results have not been confirmed in other studies. Although TPN can be successful as short-term treatment to improve nutrition and lung function e.g. prior to transplant, it has few real benefits over enteral nutrition. The cost, risk of complications and complexity of administering TPN means that it is not a routine therapy for patients with cystic fibrosis.

Parental nutrition requires a sound knowledge and application of the principle of fluid and electrolyte maintenance. Electrolyte disturbance should be corrected before introducing parenteral feeds. Biochemical elevations of aminotransferase values and alkaline phosphatase can occur 1-2 weeks after initiation of TPN and are associated with histologic change within liver cells. Steatosis or fatty liver is the most common hepatic complication of TPN in adults, whereas cholestasis is more prevalent in children. Intrahepatic cholestasis may be observed after 2-6 weeks of TPN therapy and is signalled by a rise in alkaline phosphatase followed by an elevation in bilirubin (Quigley et al, 1993 [III]).

Taurine supplemented in paediatric amino acid solutions or the administration of ursodeoxycholic acid are approaches used to promote bile flow in infants (Hofmann, 1995 [III]). Early enteral feeding is encouraged to reduce the risk and severity of cholestasis (Moss et al, 1993 [III]). In infants with persisting cholestasis, even after the cessation of TPN, the provision of exogenous cholecystokinin may reverse hepatic abnormalities (Rintala et, 1995 [III]; Teitelbaum et al, 1995 [III]).

Other complications of TPN include hyperglycaemia, hypoglycaemia, essential fatty acid deficiency, hypokalaemia and hyperlipidaemia.

## 6.14 Recommendations

- *Use of enteral and parenteral feeds should always conform to local policies and guidelines [C].*
- *Regular nutritional assessment and, when required, nutritional support should be an integral part of overall care [C].*
- *Invasive nutritional support should be considered when oral methods of maintaining an acceptable nutritional status have failed [B].*
- *Indications for nutritional support include: for children wt/ht <85%, for adults BMI<19, despite intensive use of oral supplements or a poor weight gain during pregnancy [C].*

## 6.15 Nutritional supplements (excluding desserts)

This list is correct at the time of printing. Name changes and new products occur frequently. Full details of Advisory Committee Borderline Substances (ACBS) listings for prescribable nutritional products can be found in the current edition of the British National Formulary (BNF) or MIMS. Age specific products and indications for use should be checked. Non-prescribable supplements are also available.

**Energy supplements**

*Carbohydrate*

Caloreen
Calsip
Maxijul
Polycal
Polycose
Vitajoule

*Fat and carbohydrate*

Duocal

*Fat*

Calogen
Liquigen
MCT oil

**Polymeric supplements**

*Ready to feed*

Clinutren 1.5
Clinutren Fruit
Clinutren Iso
Enlive
Enrich Plus
Ensure
Ensure Plus
Entera
Fortifresh
Fortijuice
Fortimel
Fortisip
Fortisip Multifibre
Fresubin Energy Drink
Fresubin Energy Fibre Drink
Fresubin Original Drink
Provide Xtra
Resource Protein Extra
Resource Shake

*Mix with milk*

Calshake
Scandishake

*Miscellaneous*

Pro-cal
Quickcal

**Polymeric feeds**

**1.0 kcal/ml**

- Enrich
- Ensure
- Fresubin Original
- Fresubin Original Fibre
- Fresubin 1000 Complete
- Isosource Fibre
- Isosourse Standard
- Jevity
- Nutrison Standard
- Nutrison Standard Fibre
- Osmolite
- Pro-cal
- Sondalis Fibre
- Sondalis Iso

**1.2 - 1.5 kcal/ml**

- Enrich Plus
- Ensure Plus
- Fresubin Energy Fibre
- Fresubin HP Energy
- Jevity Plus
- Novasource Forte
- Nutrison Energy
- Nutrison Energy Multifibre
- Osmolite Plus
- Sondalis 1.5

**Semi-elemental and elemental products**

- Elemental 028
- Elemental 028 Extra
- Emsogen
- MCT Pepdite
- MCT Pepdite 1+
- Novasource Peptide
- Nutrison Pepti
- Nutrison Pepti MCT
- Pepdite
- Pepdite 1+
- Peptamen
- Peptisorb
- Perative
- Survimed OPD

**Specialist feeds (this list is not exhaustive)**

- Alitraq (semi-elemental plus glutamine)
- Generaid (for use in liver disease)
- Impact (n-3 fatty acids, RNA and aginine)
- Isosource Energy (1.6 kcal/ml)
- Nutrison Concentrated (2 kcal/ml)
- Oxepa (EFA and antioxidants)
- Pulmocare (1.5 kcal/ml, low carbohydrate for respiratory disease)
- Two Cal HN (2 kcal/ml, high protein feed)

**Paediatric polymeric feeds** - these are formulated for infants or 1+ age.
(See also elemental/semi-elemental products.)

| 1.0 kcal/ml | >1.0 kcal/ml |
|---|---|
| Frebini Original | Fortini |
| Infatrini | Fortini Multifibre |
| Isosource Junior | Novasource Junior |
| Paediasure | Nutrini |
| Paediasure with Fibre | Nutrini Extra |
| Sondalis Junior (powder) | Paediasure Plus |

Nutritional products should not be used in children unless checked for suitability by a paediatric dietitian.

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# 7. NUTRITIONAL COMPLICATIONS

## 7.1 Distal intestinal obstruction syndrome

**7.1.1** Distal intestinal obstruction syndrome (DIOS), previously known as meconium ileus equivalent, is a common complication of cystic fibrosis. It is characterised by recurrent attacks of abdominal pain resulting from complete or partial intestinal obstruction and is reported to occur in between 10 to 47 percent of patients (Rosenstein & Longbaum, 1983 [III]) being more common in those over 15 years of age (Andersen et al, 1990 [III]). The syndrome is associated with faecal material and mucus gathering in the distal ileum and first part of the large intestine. The condition may present acutely as intestinal obstruction or sub-acutely with intermittent abdominal pain and constipation. There is commonly a mass palpable in the lower right abdomen. Symptoms usually respond to medical treatment; surgical treatment should be avoided if at all possible.

A number of studies have suggested that DIOS is more common in patients taking low doses of pancreatic enzyme replacement (Andersen et al, 1990 [III]). However, DIOS has also been reported in patients who are apparently pancreatic sufficient (Millar-Jones & Goodchild, 1995 [IV]). The patho-physiology is different from meconium ileus of the newborn and is incompletely understood. A number of factors may predispose to DIOS including inadequate dose of pancreatic enzymes either from inadequate prescription or poor adherence, a too rapid increase in the dose of pancreatic enzymes, dehydration as may occur in diabetes mellitus (Hodson et al, 1976 [IV]), anti-cholinergic drugs, and even addiction to opioids (Koletzko et al, 1989 [IV]). Also the intestinal abnormalities of ion secretion and motility related to abnormal cystic fibrosis transmembrane regulator (CFTR) expression are likely to be relevant (Taylor & Baxter, 1987 [IV]).

### 7.1.2 Differential diagnosis

The following should be considered in patients with CF presenting with abdominal pain: constipation with colonic overloading (Rubinstein et al, 1986 [IV]), acute intussusception (Holmes et al, 1991 [IV]), chronic intussuception (Webb & Khan, 1989 [IV]), appendicitis (Shields et al, 1990 [IV]; Coughlin et al, 1990 [IV]), fibrosing colonopathy (Smyth et al, 1994 [IV]; Littlewood, 1999 [IV]), pancreatitis (Shwachman et al, 1975 [IV]), biliary and gall bladder disease, inflammatory bowel disease (Lloyd-Still, 1990 [IV]) and complications of previous surgery (Littlewood, 1992 [IV]). It essential that other causes of abdominal pain are considered (Baxter et al, 1988 [IV]; Dalzell et al, 1990 [IV]; Littlewood, 1995 [IV]) even if the patient is known to have had previous attacks of DIOS. Patients who are having significant recurrent abdominal symptoms should have full investigation including gastrointestinal contrast studies.

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## 7.3 Cystic fibrosis related diabetes mellitus

**7.3.1** Cystic fibrosis related diabetes mellitus (CFRD) is becoming increasingly common as the median age of survival of patients with cystic fibrosis (CF) continues to rise (Hunkert et al, 1999 [III]; Lanng et al, 1991 [III]; Lanng et al, 1995 [III]). Cystic fibrosis related diabetes mellitus can be precipitated by steroid therapy or respiratory exacerbation in patients who are glucose intolerant; insulin treatment may be necessary for a short period of time.

**7.3.2** The primary aim is to maintain normal nutritional status (Moran, 1998 [III]; Wilson et al, 2000 [III]). This requires a multi-disciplinary approach, with liaison between the diabetes and CF team members. Education is vital to help both patients with CF and carers cope with a second chronic illness. Hypoglycaemia should be avoided, but control sufficient to prevent hyperglycaemia is also necessary. Dietary planning should be flexible, to meet with individual lifestyles.

### 7.3.3 Differences in the dietary management of non-CF related Diabetes Mellitus (DM) and CF Related Diabetes Mellitus (CFRD)

| | Non-CF Related Diabetes Mellitus (DNSG, 2000 [IV]) | CF Related Diabetes Mellitus |
|---|---|---|
| **Energy** | 100% of normal if the BMI (18.5 - 25). | Individualised 120 - 150% of normal. |
| **Fat** | 25 - 35% of total energy. | 40% of total energy. |
| **Refined Sugars** | Up to 10% of total energy. | Allow liberally throughout the day. |
| **Carbohydrate** | 45 - 60% of total energy. | 45 - 50% of total energy. |
| **Dietary Fibre** | Encouraged. | Encouraged in well-nourished but in poorly nourished compromises energy intake. |
| **Protein** | 10 - 20% of total energy. | 200% of Reference Nutrient Intake (RNI). |
| **Salt** | Low intake. | Increased requirement. |
| **Snacks** | Scheduled meal plan including some snacks. | Ad-lib. |

**(Adapted from Ashworth et al, 1999 [IV].)**

Conflicts between dietary therapy of CF and diabetes mellitus (DM) should always be resolved in favour of the CF diet. The energy intake should be sufficient to support normal growth in children and adolescents with CFRD, and to maintain a normal body mass index (19-25 kg/m$^2$) in adults. Patients should be advised to eat regular meals and snacks with complex carbohydrates taken at each meal e.g. bread, potatoes, pasta, cereals, in order to maintain stable blood sugars. Refined

carbohydrate, e.g. sugary drinks, which can cause a rapid rise in blood sugar if taken on their own, are best taken as part of a meal. Due to the effect of insulin deficiency on protein metabolism, protein intake should not be limited, even in patients with mild to moderate diabetic nephropathy. Consistency in timing of intake should be encouraged, and meal planning individualised to account for lifestyle, activity level, and food preference.

### 7.3.4 Conclusions.

Nutritional management is relatively straightforward for many patients with CFRD, combining the high-energy diet of CF with modifications from the DM diet. Nutritional management becomes more complicated during acute illness, hypoglycaemic episodes, or during enteral and parenteral feeding. Specialised nutritional management is best provided in a Specialist CF Centre, where a multidisciplinary CF team can work with a diabetic team that will ensure adequate attention is given to the important practical details of diabetic management.

### 7.3.5 Recommendations for routine dietary therapy of CFRD

- *Combine the elements of the cystic fibrosis and diabetes mellitus diet [C].*
- *Any dietary conflict should be resolved in favour of CF diet [C].*

(Cystic Fibrosis Related Diabetes Mellitus will be the subject of a future Cystic Fibrosis Trust Working Group consensus publication).

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## 7.5 Fibrosing colonopathy

In January 1994 the first report appeared of strictures in the proximal colon in children with cystic fibrosis (CF) (Smyth et al, 1994 [III]). Later, a case controlled study reported an association with high doses of pancreatic extract and the relatively new high strength pancreatin preparations (Smyth et al, 1995 [III]). This new disease "fibrosing colonopathy" was subsequently reported from several centres (Littlewood, 1999 [IV]).

As the problem appears dose-related, the Committee on the Safety of Medicines (CSM, 1995) recommended -
***"Pancrease HL, and Nutrizym 22 will no longer be indicated for children aged 15 years and under with cystic fibrosis, and it would be prudent for patients with cystic fibrosis not to exceed a daily dose of enzymes equivalent to 10,000 IU lipase/kg/day, regardless which preparation is used".***

For some patients following this advice may lead to unacceptable steatorrhoea; in such cases long-term acid blockade with a proton pump antagonist or even reducing the fat intake may prove helpful (Heijerman, 1992 [IIb]).

While there is no generally agreed evidence linking fibrosing colonopathy with particular enzyme preparations, concern remains over the use of Eudragit containing preparations in children. A recent review of the data concerning fibrosing colonopathy is available (Littlewood, 1999 [IV]).

A list of non-Eudragit containing pancreatin preparations, available in the UK, is given in table 3.12.

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## 7.7 Other associated disorders

Patients with enzyme requirements in excess of 10,000 IU lipase/kg/day or persisting gastrointestinal symptoms should be investigated to exclude an associated cause of malabsorption and other gastrointestinal disorders (Littlewood, 1992 [III}; Littlewood, 1995 [III]). Possible disorders include cows' milk allergy and lactose intolerance (Hill et al, 1989 [IV]), coeliac disease (Valetta & Mastella, 1989 [II]), Crohn's disease (Baxter et al, 1988 [IV], Dalzell et al, 1990 [IV]) and *C. difficile* infection (Binkowitz et al, 1999 [III]).

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# Notes

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ISBN 0-9540536-5-6

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ISBN 0-9540536-5-6