

*Australasian Clinical Practice  
Guidelines for Nutrition in  
Cystic Fibrosis*

*September 2006*

*Prepared by the Dietitians Association of Australia National  
Cystic Fibrosis Interest Group*

*Dietitians Association of Australia  
A.B.N. 34 008 521 480*

# Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis

## Foreword

These Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis have been written by dietitians who are experienced in the field of the disease in Australia and New Zealand. All Australian writers were members of the Dietitians Association of Australia (DAA) Cystic Fibrosis Interest Group.

## Writing Group

### Denise Stapleton

**Editor** (to June 2005)

Dietitian; Telethon Institute for Child Health Research;  
Women's & Children's Health Service WA

### Colleen Ash

**Chairperson**

**Co-editor** (from June 2005)

Dietitian; The Alfred VIC

### Susannah King

**Adult Co-ordinator**

**Co-editor** (from June 2005)

Dietitian; The Alfred VIC

### Evelyn Volders

**Paediatric Co-ordinator**

Dietitian; Royal Children's Hospital VIC

Christie Graham

Dietitian; Royal Children's Hospital VIC

Karen Herd

Dietitian; Prince Charles Hospital QLD

Angela Matson

Dietitian; Prince Charles Hospital QLD

Clare Collins

Dietitian; John Hunter Hospital NSW

### With contributions also from

Maggie Aitken

Dietitian; Sydney Children's Hospital NSW

Aurora Avedill

Dietitian; Royal Prince Alfred Hospital, NSW

Julia Boase

Dietitian; Women's and Children's Hospital SA

Melissa Carr

Dietitian; John Hunter Hospital NSW

Tory Crowder

Dietitian; Auckland City Hospital, New Zealand

Vicki McWilliam

Dietitian; Royal Children's Hospital VIC

Marina Keating

Dietitian; Princess Margaret Hospital WA

Clare Klimes

Dietitian; The Children's Hospital at Westmead NSW

Kathryn Marshall

Dietitian; The Alfred VIC

Catherine Painter

Dietitian; Royal Adelaide Hospital SA

Marcelle Pappas

Dietitian; Women's and Children's Hospital SA

Clare Rawcliffe

Dietitian; St Vincent's Hospital NSW

Indi Swan

Dietitian; The Alfred VIC

Prue Watson

Dietitian; The Children's Hospital at Westmead NSW

Our thanks are extended to the following professionals for their valuable comments and suggestions upon reviewing the document:

Dr Scott Bell, Respiratory Physician,  
Professor Peter Sly, Paediatric Respiratory Physician  
Associate Professor Duncan Topliss, Endocrinologist

# Table of Contents

Foreword.....	ii
Table of Contents.....	iii
List of Tables.....	vi
List of Abbreviations.....	vi
Executive Summary.....	vii
1. Introduction.....	1
1.1 Background to the guidelines.....	1
1.2 Purpose and scope.....	1
1.3 Consultation process.....	2
1.4 Methods.....	3
1.5 Review process.....	5
1.6 Applicability.....	6
1.7 Editorial independence.....	6
2. Nutritional issues in CF.....	7
2.1 Background.....	7
2.2 Role of nutrition.....	7
2.3 Aetiology of malnutrition.....	8
2.3.1 Increased energy expenditure.....	8
2.3.2 Maldigestion, malabsorption & other losses.....	9
2.3.3 Inadequate intake.....	9
2.3.4 Co-morbidities.....	10
2.4 The inter-relationship between nutrition & pulmonary disease.....	10
2.5 Barriers to optimal intake.....	11
2.5.1 Knowledge.....	11
2.5.2 Behaviour.....	11
2.5.3 Complexity of the treatment.....	12
2.6 Specialist CF management.....	12
2.6.1 Specialist dietetic CF management.....	12
2.6.2 Staffing requirements.....	13
Recommendations.....	14
3. Nutritional assessment in CF.....	15
3.1 Background.....	15
3.2 Measurement of height, weight & head circumference.....	15
3.2.1 Techniques & standards for measurement.....	15
3.2.2 Frequency of measurement.....	16
3.2.3 Indices of nutritional status.....	16
3.2.4 Body composition.....	17
3.3 Dietary intake.....	18
3.3.1 Methods for assessment.....	18
3.3.2 Frequency.....	19
3.3.3 Scope.....	19
3.4 Biochemical assessment.....	19
3.4.1 Methods & frequency.....	19
3.5 Other assessment factors.....	23
Recommendations.....	23
4. Nutritional requirements in CF.....	24
4.1 Background.....	24
4.2 Macronutrients.....	24
4.2.1 Energy.....	24

4.2.2 Fat .....	24
4.2.3. Protein .....	25
4.2.4 Carbohydrate .....	25
4.2.5 Fibre .....	26
4.3 Vitamins .....	26
4.3.1 Prevalence of deficiency .....	26
4.3.2 Factors contributing to deficiency .....	26
4.3.3 Monitoring of vitamin status .....	26
4.3.4 Supplementation .....	27
4.3.5 Vitamin A .....	28
4.3.6 Vitamin D .....	29
4.3.7 Vitamin E .....	30
4.3.8 Vitamin K .....	30
4.3.9 Water-soluble vitamins .....	31
4.4 Minerals .....	31
4.4.1 Sodium and fluids .....	31
4.4.2 Iron .....	33
4.4.3 Calcium .....	34
4.5 Other nutritional factors .....	34
4.5.1 Antioxidants .....	34
4.5.2 Essential fatty acids .....	35
4.5.3 Probiotics .....	35
4.5.4 Complementary therapies .....	36
Recommendations .....	36
5. Implementing nutritional management of CF .....	38
5.1 Introduction and rationale for nutritional management .....	38
5.2 Pancreatic enzyme replacement therapy (PERT) .....	39
5.2.1 Introduction .....	39
5.2.2 Indications for PERT .....	39
5.2.3 Prescription and dosing of PERT .....	39
5.2.4 Evaluating pancreatic function and monitoring efficacy of PERT .....	40
5.3 Criteria for nutritional intervention .....	42
5.4 Routine management of oral intake .....	46
5.4.1 Dietary guidelines .....	46
5.4.2 Infants .....	46
5.4.3 Children .....	48
5.4.4 Adolescence .....	49
5.4.5 Transition to adult care .....	49
5.4.6 Adults .....	49
5.4.7 Education .....	50
5.4.8 Inpatient management .....	51
5.5 Oral nutritional supplements .....	51
5.5.1 Background .....	51
5.5.2 Use .....	52
5.5.3 Monitoring .....	52
5.6 Appetite stimulants .....	53
5.7 Enteral feeding .....	53
5.7.1 Benefits .....	53
5.7.2 Route .....	54
5.7.3 Complications .....	54
5.7.4 Amount .....	54
5.7.5 Type .....	54
5.7.6 PERT .....	55
5.8 Parenteral nutrition .....	55

Recommendations.....	56
6. Management of gastro-intestinal & hepato-biliary complications.....	58
6.1 Meconium ileus.....	58
6.2 Distal ileal obstruction syndrome.....	58
6.3 Constipation.....	58
6.4 Fibrosing colonopathy.....	58
6.5 Gastro-oesophageal reflux.....	59
6.6 Liver disease.....	60
6.7 Pancreatitis.....	60
Recommendations.....	61
7. Cystic fibrosis-related diabetes.....	62
7.1 Prevalence & impact of cystic fibrosis-related diabetes.....	62
7.2 Diagnosis & screening.....	62
7.3 Medical management.....	63
7.4 Nutritional management.....	65
7.5 Enteral feeding.....	66
Recommendations.....	66
8. Osteoporosis.....	67
8.1 Prevalence & aetiology.....	67
8.2 Assessment of bone mineral density.....	67
8.3 Management.....	68
Recommendations.....	69
9. Pregnancy.....	70
9.1 Pregnancy outcome.....	70
9.2 Nutritional assessment & counselling.....	70
9.2.1 Overview.....	70
9.2.2 Vitamin A.....	70
9.2.3 Folate.....	71
9.2.4 Food safety.....	71
9.2.5 Gestational CFRD.....	71
9.2.6 Additional nutritional support.....	71
9.2.7 Lactation.....	72
Recommendations.....	72
10. Lung transplantation.....	73
10.1 Impact of nutritional status.....	73
10.2 Nutritional management prior to lung transplantation.....	73
10.3 Nutritional management post-lung transplantation.....	74
10.4 Impact of post-lung transplantation co-morbidities.....	75
Recommendations.....	76
11. Implementation & evaluation of the Guidelines.....	77
11.1 Implementation plan.....	77
11.2 Evaluation plan.....	77
11.3 Recommendations for research.....	77
Appendices.....	78
Appendix 1: National dietetic service provision within CF facilities across Australia, 2004.....	78
Appendix 2: Australian Guidelines for Pancreatic Enzyme Replacement Therapy.....	80
Appendix 3: Pancreatic enzyme products available in Australia.....	81
Appendix 4: Recommendations for the use of PERT with enteral tube feeding.....	82
Appendix 5: Behavioural change.....	83
Appendix 6: Writing group declarations.....	84
References.....	85

## List of Tables

Table 1: Levels of Evidence used in the Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis .....	5
Table 2: Suggested minimum frequency for recording anthropometric measurements .....	16
Table 3: Dietary factors to assess in individuals with CF .....	19
Table 4: Biochemical monitoring of nutritional status in individuals with CF .....	20
Table 5: Recommended starting doses for vitamin supplementation in individuals with CF .....	27
Table 6: Composition of VitABDECK® .....	28
Table 7: Doses of vitamins A, D & E in preparations commonly available in Australia & New Zealand .....	28
Table 8: Anthropometric criteria indicating nutritional intervention that may be required <sup>1</sup> .....	44
Table 9: Australian dietary guidelines for children and adolescents, including those with cystic fibrosis .....	46
Table 10: Australian dietary guidelines for adults, including those with cystic fibrosis .....	50

## List of Abbreviations

BMI	Body mass index
BMD	Bone mineral density
CF	Cystic fibrosis
CFRD	Cystic fibrosis-related diabetes
CRP	C-reactive protein
DAA	Dietitians Association of Australia
DXA	Dual x-ray absorptiometry
DIOS	Distal intestinal obstruction syndrome
EFA	Essential fatty acids
EFT	Equivalent full time
FEV <sub>1</sub>	Forced expiratory volume in 1 second
GOR	Gastro-oesophageal reflux
IBW	Ideal body weight
IGT	Impaired glucose tolerance
IU	International units
NHMRC	National Health and Medical Research Council
NZ	New Zealand
OGTT	Oral glucose tolerance test
PERT	Pancreatic Enzyme Replacement Therapy
REE	Resting energy expenditure
RDI	Recommended daily intake
UK	United Kingdom
USA	United States of America

## Executive Summary

Cystic fibrosis (CF) is the most common lethal genetic disease in the Caucasian population, affecting approximately 1 in 2500 live births. Approximately 3000 people with the disease live in Australia and New Zealand (NZ) [1].

CF is a multi-system disorder. Its clinical manifestations include chronic obstructive lung disease; exocrine pancreatic insufficiency; intestinal obstruction; failure to thrive and malnutrition; and abnormally high sweat sodium and chloride levels. Optimal management of CF involves numerous treatment modalities. A multidisciplinary approach at a specialised care centre is recommended [2-5] and appears to be associated with improved outcomes [6, 7]. Treatment of CF includes antibiotic therapy, mucolytic and bronchodilator therapy, airway clearance, exercise and nutritional therapy [2]. The aim of treatment is to improve the duration and quality of life of the individual.

Optimal nutrition and normal growth are now identified as realistic goals for everyone with CF [8]. However, despite significant improvements in the nutritional status of CF populations over recent decades, nutritional failure is still a common problem for people with CF. The aetiology of malnutrition in CF is complex and multifactorial, including inadequate dietary intake, malabsorption and elevated energy expenditure [9]. Recently, a number of international and country-specific bodies have published guidelines for nutrition in CF [8, 10, 11]. After review of these documents, it was decided to develop Australasian guidelines for best practice in the nutrition management of CF, in order to address the unique aspects of nutrition care that may not be relevant elsewhere. For example, issues related to sodium intake in hot climates and to supporting isolated or sole practitioners are likely to require different emphasis. The purpose of these guidelines is to outline the key nutrition issues that people with CF face and to provide dietetic practitioners and CF clinicians with clear, evidence based recommendations to address these issues.

The key clinical question that this document addresses is:

**“What is the role and scope of nutritional care in the management of CF?”**

Evidence statements that address this question included those that are listed below.

<b>Evidence statement</b>	<b>Evidence level</b>
Poor nutritional status is an independent risk factor for poor survival in CF.	C [12-15]
Deterioration in parameters of nutritional status should be detected early, before growth and pulmonary function are compromised.	C [10]
The significant improvements in the nutritional status of CF populations have been attributed, in part, to changes in dietary recommendations to unrestricted fat diets.	C [15, 16]
Deficiencies of fat-soluble vitamins have been demonstrated in individuals with CF, particularly in those with pancreatic insufficiency	B [17, 18]
Fat-based dosing of pancreatic enzyme replacements therapy (PERT) has been shown to lead to a significant improvement in fat absorption in CF.	C [19]
Enteral feeding in malnourished individuals with CF has been associated with positive nutritional outcomes.	C [20-25]
Concurrent diseases, such as cystic fibrosis-related diabetes, liver disease and gastro-oesophageal reflux, may also contribute to poor nutritional status in CF.	D [9, 26]

A minimum dietetic service provision of 0.4 equivalent full time (EFT) per 50 CF patients receiving full time care should be allocated	D [39, 121]
--	-------------

Some of the key practice recommendations in the guidelines are outlined below.

### **Practice recommendations**

1. The CF management team should include an experienced dietitian to undertake nutritional assessment; provide education and individualised advice; ensure communication of nutrition issues with the CF team; and conduct nutritional surveillance, audits and research intervention on all individuals with CF.
2. Periodic nutritional assessments should encompass a collation of anthropometric, dietary, biochemical and relevant clinical data.
3. Energy requirements in individuals with CF are likely to be between 120 to 150% greater than healthy individuals. Encourage a diet unrestricted in fat to meet energy requirements.
4. Serum levels of fat soluble vitamins A, D and E should be measured routinely in all individuals with CF, particularly those with pancreatic insufficiency, and supplementation commenced if levels are below reference ranges.
5. In individuals with pancreatic insufficiency, use the *Pancreatic Enzyme Replacement Therapy (PERT) in Cystic Fibrosis: Australian Guidelines* (including fat-based dosing) to prescribe PERT and monitor efficacy.
6. The provision of supplementary nutrition via enteral tube feeding should be considered when other avenues of nutrition support have failed, and the patient meets criteria for nutritional failure.
7. Identification and management of nutrition-related co-morbidities, including cystic fibrosis-related diabetes, liver disease, gastro-oesophageal reflux and osteoporosis is an essential component of comprehensive nutritional care.

These practice guidelines will be disseminated amongst dietitians working in CF centres in Australia and NZ, and made available to other health professionals working in the CF field. They will be made available on the DAA website for all DAA members to access and utilise.

The guidelines will be due for review in 2011.

# 1. Introduction

## 1.1 Background to the guidelines

Nutritional failure is still a common problem for people with cystic fibrosis (CF). This is despite recommendations that optimal nutrition and normal growth is a realistic goal for everyone with CF [8]. The first step in rectifying this major problem is for CF clinics to have clear nutrition recommendations. While these have been developed for populations in the USA, Europe and the UK it is important to have regional guidelines [8, 10, 11]. This helps to address the unique aspects of nutrition care that may not be relevant elsewhere. For example, issues related to sodium intake in hot climates and to supporting isolated or sole practitioners are likely to require different emphasis. These guidelines are intended to outline the key nutrition issues that people with CF face and to provide dietetic practitioners and CF clinics with clear, evidence based recommendations to address such issues.

In addition, a survey of CF centre dietitians that was undertaken in 2003 as a repeat of the survey conducted in 1995 indicated practice variations (n= 17, 9 paediatric centres, 5 adult centres, 3 both) [27]. Seventeen centres completed the survey (9 paediatric, 5 adult, 3 both) [28]. Practice varied in the following areas: calculation of energy requirements; monitoring of nutritional status; age at which solids are introduced; pancreatic enzyme dosage; use of enzymes with enteral feeds; methods of salt supplementation and criteria for the commencement of oral supplements and enteral feeding. The dietitians that responded were mostly in agreement that the barriers to optimal nutritional status included poor appetite, chronic lung infections, behavioural/psychological problems and malabsorption [28].

The guidelines cover definitions and assessment of malnutrition, nutritional status and degrees of nutrition failure, management of nutrition issues, oral and enteral nutrition support and concurrent problems and strategies to improve adherence to recommendations. The recommendations documented in these Australasian Guidelines are based on evidence up to and including 2005. Where there is a lack of strong evidence, the different approaches to the CF-related nutritional issues in Australasia are presented. The number of discrepancies regarding the management of nutrition in CF is likely to reduce during the development, utilisation and on-going evaluation of these guidelines. We have shown in the past that having Australian clinical guidelines for pancreatic enzyme replacement therapy (PERT) [29, 30] has reduced the discrepancies in the approach to management [31]. The aim of the Australian and New Zealand (NZ) nutrition guidelines is to help improve nutritional status and quality of life for people with CF and their families.

## 1.2 Purpose and scope

The goal of the Guidelines is to optimise the nutritional status of all infants, children and adults with CF in Australasia.

The objectives of the Guidelines are to:

1. Optimise the assessment of nutritional status in order to detect deterioration early.
2. Optimise the management of nutrition and PERT, including the management of concurrent diseases and other relevant issues.
3. Achieve and maintain adequate nutritional status.

The purpose of the Guidelines is to:

1. Provide a current best-practice nutrition and PERT reference for all health professionals, providing care to individuals with CF and their families.

2. Ensure the nutritional and PERT care provided to all infants, children and adults with CF is evidenced-based, where possible, and reflects current knowledge.
3. Standardise the nutritional and PERT care of infants, children and adults with CF.
4. Be widely and readily available in order to support isolated practitioners.
5. Promote nutritional and PERT care as a priority in service provision to individuals with CF.

#### Scope of the guidelines:

The target population of these Guidelines is Australian and NZ residents who have been diagnosed with CF. The document is intended to be applicable across all age groups within the CF population. Differences in nutritional and health-related issues, management or recommendations for different age groups, disease stages or geographical conditions within the target countries are indicated within the document, or addressed separately for different groups.

The Guidelines are intended as a resource that covers the many aspects of nutrition management of CF and the role of the dietitian in providing care to individuals with CF. They address clinical questions including, but not limited to:

- What is the role of nutritional care in the management of CF?
- What are the key components of nutritional assessment in CF?
- What are the nutritional requirements for optimal growth and development in children with CF and optimal nutritional status in adults?
- How should fat-soluble vitamin deficiencies be detected, prevented and treated?
- How should PERT be prescribed for individuals with CF who are pancreatic insufficient?
- What are the criteria for classifying an individual with CF as having acceptable nutritional status, at-risk nutritional status, or malnutrition, and what are the appropriate interventions for each stage?
- What are the key components of routine nutritional management in CF, and how should they be implemented?
- When and how should nutrition support (oral, enteral and parenteral) be instituted in individuals with CF?
- What is the role of nutritional management in the key co-morbidities affecting individuals with CF?
- What impact does pregnancy have on the nutritional management of CF?
- What impact does lung transplantation have on the nutritional management of CF?
- What is the level of dietetic practice required for CF patients?

### ***1.3 Consultation process***

<b><i>Time</i></b>	<b><i>Stage</i></b>
August 2003	Australasian Cystic Fibrosis Conference, Melbourne: workshop to discuss guideline development at Dietitians Association of Australia (DAA) CF Interest Group meeting. Assignment of chairperson and adult and paediatric co-ordinators. Preliminary discussion of areas to be addressed in the guidelines amongst attending dietitians who volunteered to contribute. Allocation of topic areas to each contributor.
September 2003 – August 2004	Additional dietitians co-opted as contributors to specific areas. Contributing dietitians reviewed literature and developed draft recommendations.
October 2004	Appointment of editor and establishment of writing group. Dietitians working in the area of CF in Australia and NZ were invited to express interest in becoming a member of the writing group. Those who responded to this expression of interest, and were able to commit to the timelines, formed

the writing group. All members of the writing group have extensive experience in clinical dietetic service delivery and/or nutrition research in the area of CF.

- November 2004 – April 2005 Members of the writing group and editor produced draft guideline document which was then reviewed and revised by the whole group.
- May – July 2005 Draft document offered to stakeholders for comment, including CF Clinic dietitians in Australasia, DAA CF Interest Group members, other health professionals involved in CF care\* and the CF support organisation\*\*.
- August 2005 DAA CF Interest Group workshop held in conjunction with the 5<sup>th</sup> Australian and NZ CF Conference, Adelaide, 21 August 2005. This group represents the key group of target users. Workshop included:
- Summary of draft guideline document
  - Areas of disagreement highlighted
  - Key recommendations for in-depth discussion highlighted (e.g. assessment recommendations, criteria for nutrition intervention)
  - Feedback sought on areas of disagreement and key recommendations, following discussion and consensus via small break-out groups
- August – November 2005 Revisions of draft guidelines document by writing group members, incorporating comments and feedback from stakeholders who were offered the draft document, and from CF Interest Group workshop. The individuals who provided feedback and comment are acknowledged on page i. No comments were received from the CF support organisation.
- March – July 2006 Further consultation and feedback sought from writing group members; dietitians working in CF; physicians working in area of CF; and consumers. Consumer feedback was sought through the Consumer Advisory Committee of Cystic Fibrosis Victoria (Inc), the support and advocacy organisation for individuals with CF in Victoria. Comments and feedback received from these groups were incorporated into final version of the guidelines. This included comments made by two lay consumers as part of consultation with the Consumer Advisory Committee of CF Victoria (Inc).
- \* achieved via invitation to CF respiratory physicians extended at the TSANZ meeting in March 2005, the major annual Australasian meeting attended by this professional group; and by contact with other health professionals involved in the management of individuals with CF (e.g. endocrinologists).
- \*\* Cystic Fibrosis Australia, the umbrella organisation for the state-based patient groups.

## **1.4 Methods**

The literature search for this document was conducted by the use of electronic databases, including MEDLINE, hand-searching journals, reviewing conference proceedings and assessing other guidelines [2, 8, 10, 32]. The searches were limited to the English language and primarily to the year 2000 onwards, but original papers were reviewed and are cited where applicable, and older papers included for review where there was an absence of recent literature. Literature up to 2005 has been included. Evidence from less rigorous research and expert opinion are included, and

identified as such, as many of the parameters involved in assessing nutritional status are difficult to assess and have not been conclusively determined.

The criteria for grading the evidence cited in the guidelines are based on the NHMRC levels of evidence and are listed in Table 1.

The recommendations were formulated by general agreement among dietitians with experience in the area of CF and based on the evidence available. During the draft revision process by the writing group members, a consensus model was used to achieve a recommendation that all group members agreed with. Where agreement was not reached, a ballot was conducted of writing group members. There were no areas of disagreement amongst the writing group with the final recommendations. For some aspects of management there is a lack of definitive evidence for one strategy over another. In such cases, the alternative approaches to management are presented within the Guidelines.

Table 1: Levels of evidence used in the Australasian clinical practice guidelines for nutrition in cystic fibrosis (adapted from the National Health and Medical Research Council (NHMRC) levels of evidence [33]).

Evidence Category - Level	Sources of Evidence	Definition and NHMRC equivalent
A – High  Substantial numbers of studies involving substantial numbers of participants	Randomised controlled trials (RCTs) (rich body of data)	Evidence is from endpoints of well-designed RCTs or trials that depart only minimally from randomisation, that provide a consistent pattern of findings in the population for which the recommendation is made  NHMRC Level I: Systematic review of RCTs
B – Medium  Generally few RCTs, small in size, results inconsistent, or undertaken in a population that differs from the target population of the recommendation	RCTs (limited body of data)	Evidence is from endpoints of intervention studies that include only a limited number of RCTs, post hoc or subgroup analysis of RCTs, or meta-analysis of RCTs.  NHMRC Level II At least one well designed RCT  NHRMC Level III-1: A pseudo-randomised RCT  NHMRC Level III-2 Non RCTs e.g. cohort or case-controlled studies
C – Low  Some evidence to support but quality is low	Non-randomised trials, observational studies	Evidence from outcomes of uncontrolled or non-RCTs or observational studies  NHMRC Level III-3 Controlled studies with historical control  Level IV Evidence from case series, pre-test/post-test
D – Opinion  Category used where provision of some guidance is needed but there is a gap in the research addressing the subject of the recommendation	Expert opinion	Expert judgement based on synthesis of evidence from experimental research reported in the literature and/or derived from expert consensus based on clinical experience or knowledge that does not meet the above-listed criteria.  NHMRC do not ascribe an evidence level to expert opinion

### 1.5 Review process

The Guidelines will be due for review and updating in 2011, incorporating new evidence and results of evaluation of the Guidelines (see also section 11.2).

## ***1.6 Applicability***

Implementation of the recommendations detailed in the Guidelines will be limited by dietetic time allocated to CF. For example, implementation of a preventative nutrition program like *Go and Grow with CF* [34] is dependent on adequate dietetic time allocation, which is two and a half hours per child over three months. The extra time invested in conducting a preventative nutrition program is likely to reduce the demands on dietetic staff of ad hoc problem solving, resulting in better use of expertise [34]. These Guidelines include discussion regarding recommended staffing resource allocation for CF and highlights that dietetic input in Australasian CF centres is under-resourced.

At the time the draft document was prepared, most CF services in Australasia had levels of dietetic staffing that did not meet previously published recommendations (see Appendix 1). Under-staffing will potentially limit the degree to which individual CF services are able to implement the guidelines. During the period between the original draft of the guidelines and the finalised version, a number of key stakeholders in the CF field have sought to use the information in the draft guidelines to advocate for increased dietetic resources. In at least one case, towards the end of 2005, a service has been successful in achieving increased funding to match the staffing recommendations outlined in section 2.6.2. The finalised Guidelines have the potential to be used by dietitians and other stakeholders to lobby for adequate dietetic staffing, which will facilitate full implementation of the recommendations in the Guidelines.

In May 2005, between the original drafting of the guidelines, and finalisation, a survey of current dietetic practice and management of CF in Australia and New Zealand was conducted. As at March 2006, the results of the survey are being written up for a separate publication. The survey responses covered approximately 80% of the CF centres, and indicate that current practice in most key areas is relatively consistent with the recommendations in the Guidelines. However, dietetic staffing was generally considered by respondents to be inadequate. Key areas of inconsistency between practice and the recommendations included:

- dietary assessment
- lack of criteria for institution and cessation of oral nutritional supplements and enteral nutrition
- funding of oral and enteral nutrition support, which differed across states of Australia
- diabetes screening and management

The results of this survey will provide essential baseline data for monitoring and auditing the implementation of the Guidelines. In States and/or CF services in which the cost of nutrition support is not funded or subsidised, the Guidelines have the potential to be used as part of a process to advocate for funding towards the cost of these interventions, thereby reducing inequities in service provision.

## ***1.7 Editorial independence***

Development of the Guidelines has been sponsored in part by an education grant awarded by Cystic Fibrosis Australia (made available by Technipro Marketing Pty Ltd), a grant from Solvay Pharmaceuticals and finance from Nutricia Australia. The views or interests of these funding bodies have not influenced the recommendations. The DAA CF Interest Group workshops conducted in 2003, 2004 and 2005, at which the Guidelines development was one of the agenda items, were externally sponsored. The views or interests of the workshop sponsors have not influenced the final recommendations.

Writing group conflict of interest and funding declarations are outlined in Appendix 6.

## **2. Nutritional issues in CF**

### **2.1 Background**

CF is the most common lethal genetic disease in the Caucasian population, affecting approximately 1 in 2500 live births. Approximately 3000 people with the disease live in Australia and New Zealand [1]. Survival largely depends on the rate of progression of lung disease, with most individuals dying of cardio-respiratory failure. Survival has improved substantially over recent decades, with the current predicted median survival being 35 years of age [35].

Clinical features of CF include chronic obstructive lung disease and abnormally high sweat sodium and chloride levels, due to failure of salt reabsorption in sweat gland ducts. Other features may include steatorrhea and azotorrhea, due to exocrine pancreatic insufficiency, intestinal obstruction in the neonate or older patient, failure to thrive and malnutrition, chronic sinusitis, cirrhosis of the liver, clubbing of the extremities, osteopenia, episodic arthritis and infertility [2]. Although the pathogenesis of CF is increasingly understood, no specific therapy is available to correct the genetic defect, and treatment is limited to dealing with complications that arise. The complexity and progressive nature of CF means that optimal management may not always lead to good medical outcomes.

Approximately 80-100 new diagnoses of CF are made annually in Australasia [1]. Some individuals with CF present with meconium ileus at birth, and are subsequently diagnosed with CF within the first few days of life. The majority of new diagnoses are made via newborn screening programs. All states of Australia, and New Zealand, have community-wide newborn screening programs for CF, resulting in the diagnosis being made for individuals who did not present with meconium ileus at birth, at approximately 4-6 weeks of age. A blood specimen obtained from a heel-prick of an infant within a few days of birth is tested for levels of immunoreactive trypsinogen [36]. Samples with immunoreactive trypsinogen levels above the 99<sup>th</sup> percentile are tested for the presence of a gene mutation characteristic of CF. Those who have two copies of the gene mutation are diagnosed with CF, while those with one copy are recalled for a sweat test. A positive result (sweat chloride  $\geq$  60mmol/L) is consistent with a diagnosis of CF [36]. A small number of individuals are diagnosed with CF at a later age, having presented with clinical features of CF, either because they were born before the implementation of newborn screening, or were not detected by such a program. Following the diagnosis of CF, a referral is made to a CF physician [36] (see section 2.6).

Being a multi-system disease, optimal management of CF involves numerous treatment modalities. A multidisciplinary approach at a specialised care centre is recommended [2-5] and appears to be associated with improved outcomes [6, 7] (evidence category C). Comprehensive discussions regarding the overall management of CF are available [2, 37, 38]. In brief, treatment of CF includes antibiotic therapy, mucolytic and bronchodilator therapy, airway clearance, exercise and nutritional therapy [2]. The aim of treatment is to improve the duration and quality of life of the individual.

### **2.2 Role of nutrition**

The importance of nutritional care in the management of CF is well recognised and the care team should include a dietitian who has specialised in the disease [2, 3, 12, 39]. Poor nutritional status is an independent risk factor for poor survival [12-15] (evidence category C) and has also been associated with complications of CF, including reduced bone mineral density (BMD) [40-45] (evidence category C).

There is evidence that nutritional deficits are present from an early age in individuals with CF, even in those identified through newborn screening programs [46-49]. One of the benefits of early diagnosis and treatment is that nutritional status is better in children diagnosed through newborn screening programs than those with later diagnosis. Nutritional deficits have been observed in non-screened individuals until at least 13 years of age [46, 47] (evidence category B). Also, an association between nutritional deficits at diagnosis and cognitive function has been observed up until 17 years of age [50].

Progressive or episodic deterioration in growth and nutritional status has been noted to occur in some sub-groups of those with CF [51-55] (evidence category C). Early identification and management of growth retardation have the potential to optimise pulmonary function, as poor growth may be associated with defective lung growth [52, 53]. The significant improvements in the nutritional status of CF populations over recent decades [56] have been attributed, in part, to changes in dietary recommendations from low fat to unrestricted fat diets [15, 16] (evidence category C) and early diagnosis through newborn screening programs [47, 57].

Despite the improvement, malnutrition continues to be a major clinical problem in individuals with CF as is evident in the retardation in weight gain and linear growth of most patient populations. For example, data from the Australasian CF Data Registry from 2002 indicate that 12% of children and adolescents were below the 5<sup>th</sup> percentile for height, and 10% were below the 5<sup>th</sup> percentile for weight [1]. The impact of CF on growth during childhood and adolescence is demonstrated by the trend towards lower mean height and weight Z-scores in older age groups compared with those in infants and young children [1]. Underweight remains prevalent in adults as well as children, with 8% of adults having a body mass index (BMI) <18 kg/m<sup>2</sup>, and a further 23% with a BMI between 18 and 20 kg/m<sup>2</sup> [1].

## **2.3 Aetiology of malnutrition**

Most of the signs of malnutrition in CF (weight deficits, growth retardation, delayed bone age, loss of adipose tissue, muscle wasting, hypoalbuminemia, oedema, anaemia, bruising, bleeding, immune and respiratory dysfunction, developmental delay and delayed puberty) can be related to a protein-energy deficit or the malabsorption of essential nutrients [9, 58]. Energy deficits may arise as a consequence of CF-related increases in energy expenditure, increases in gastrointestinal losses and decreases in oral intake. In addition to inadequate energy, macro- and micronutrient deficiencies (due to decreased intake, increased utilisation and gastrointestinal losses), lung infections and concurrent diseases can also affect growth and overall nutritional status. Other conditions that impact on diet and nutritional status include CF related diabetes (CFRD), pregnancy in women with CF and lung transplantation.

### **2.3.1 Increased energy expenditure**

Increased energy expenditure arises from a combination of lung infection and inflammation (through oxidant injury and inflammatory mediators), the increased work of breathing and coughing and the stimulation of metabolism by bronchodilator therapy [59, 60]. Reported mean elevations in resting energy expenditure (REE) in individuals with CF are in the range of 5-30% over healthy controls [52, 59-66] (evidence category B), although there is wide variation and no clear correlations with clinical parameters such as pulmonary function in most studies. Increased REE is not thought to be attributable to a primary defect in energy metabolism [67], as elevations in basal metabolic rate or total energy expenditure were not observed in young infants with lung disease aged <20 weeks [49] (evidence category B). Other studies investigating total daily energy expenditure in CF indicate that levels are not elevated, most likely because individuals can compensate for raised REE by reducing their level of physical activity, such that those with

moderate lung disease have comparable total daily energy expenditure to controls [68-70] (evidence category B).

### **2.3.2 Maldigestion, malabsorption & other losses**

Maldigestion, and hence malabsorption of nutrients, due to exocrine pancreatic insufficiency, reduced bile salt pool and increased intestinal mucus is experienced by 85-90% of individuals with CF [9, 37, 71]. Maldigestion in CF affects energy and protein availability, as without treatment, gastrointestinal losses of fat and nitrogen are severe. Growth may be limited by the subsequent energy and protein deficit and related increase in protein catabolism [9]. Maldigestion of various micro-nutrients may also inhibit growth directly, or indirectly through the effects of specific deficiencies on pulmonary function and immunity [17]. Gastrointestinal problems associated with maldigestion and malabsorption, such as abdominal pain, can affect nutritional status indirectly by decreasing appetite [72].

Individuals with CF-related pancreatic insufficiency require long-term PERT to treat macro- and micronutrient maldigestion [56]. The aim of PERT is to minimise the incidence of frequent, loose, bulky, foul-smelling, greasy stools, rectal prolapse, hypoalbuminemia, oedema, anaemia and azotorrhea, which are commonly experienced before diagnosis. Refinements in pancreatic enzyme preparations over the past two decades have improved fat absorption [73], such that, together with a high fat diet, growth and nutritional status in CF have significantly improved [15, 16] (evidence category C). However, even though the currently used enteric-coated, encapsulated micro spheres are generally considered to have superior efficacy when compared to previous preparations [74], normal fat absorption does not appear to have been achieved by the majority of individuals on PERT, as indicated by several studies of subgroups of CF populations [75-79] (evidence category C).

Faecal losses continue to be high and may account for approximately 5 to 20% of gross energy intake in subjects with CF compared with 3 to 4 % in controls [80] (evidence category B). It is possible that persistent fat malabsorption despite PERT may be related to defects in solubilisation or absorption of digested fats rather than to inadequate provision of lipase via PERT [75] (evidence category D). The achievement of optimal PERT in individuals with CF would not only reduce maldigestion and malabsorption, but also ensure that the adverse effects of associated abdominal pain on appetite are minimised [72].

It is possible that protein digestion in individuals receiving PERT also remains sub-optimal as stool nitrogen output appears to be increased [81]. However, this may be more a reflection of rapid colonic transit and antibiotic usage than an indication of the degree of protein digestion [81].

Small amounts of energy and nitrogen may also be lost from the body through the expectoration of sputum. Wootton et al [60] estimated this loss to be 1 to 5% of gross energy intake in five patients with CF during a period of hospitalisation related to an infectious exacerbation (evidence category C).

### **2.3.3 Inadequate intake**

Dietary inadequacy is likely to contribute significantly to poor nutritional status throughout life [17]. The extent to which nutrient inadequacies contribute to unfavourable energy balance is difficult to determine as the validity of measurements is uncertain and the specific requirements for CF are not known. For example, protein intakes of individuals with CF are commonly in excess of the recommended dietary intake (RDI) for age and gender [16, 82, 83] (evidence category C), a finding similar to that observed in the general population), but it is not known what level is sufficient to counter the effects of the disease as RDIs are developed for the general population, which mostly includes well individuals [84].

Recommendations for individuals with CF have targeted an energy intake of between 120 and 150% of normal energy requirements for age and gender to compensate for elevated energy expenditure and losses [85, 86]. Several studies indicate that intakes continue to be well below the elevated energy recommendation, with mean levels ranging from 92 to 115% of the RDI [42, 60, 78, 82, 83, 87-91] (evidence category C). Powers [92] found that only 11% of infants and toddlers met their theoretical elevated energy requirement and that fat intakes did not meet the recommended level of 40% of energy intake, being only 34% of their energy intake.

It is important to note that the validity of studies reporting dietary intake is limited by methodological issues (dietary data collection method, representativeness of usual intake, type of food composition tables) [93] and differences between the CF populations (including age and disease severity).

Lastly, inflammation may contribute to decreased appetite due to the release of cytokines by immuno-competent cells. This is a particular problem during a pulmonary exacerbation where inflammation increases and energy intake is suppressed. Appetite has been shown to be stimulated following antibiotic treatment [94, 95].

#### **2.3.4 Co-morbidities**

Concurrent diseases, such as CFRD, liver disease and gastro-oesophageal reflux (GOR), may also contribute to the energy imbalance and poor nutritional status of those with CF [9, 26], particularly prior to diagnosis and adequate treatment (evidence category D). Pancreatic impairment is often progressive and approximately 31% of older individuals develop CFRD [96] (evidence category C). If untreated, or inadequately controlled, diabetes can contribute to energy deficits through glycosuria [9]. In addition, liver disease may exacerbate the severity of malabsorption through inadequate bile acid secretion [9, 10]. Other gastrointestinal complications (distal-intestinal obstruction syndrome, constipation, oesophagitis and chronic abdominal pain) may also make significant contributions to malnutrition in CF [9, 26].

#### **2.4 *The inter-relationship between nutrition & pulmonary disease***

The inter-relationship between the CF disease process, infection, lung disease and malnutrition is complex, and there is a lack of evidence to demonstrate a causal relationship [9]. Chronic lung infection can contribute to weight loss by increasing REE and decreasing protein synthesis [97]. The metabolic effects of stress hormones and immune factors secreted during lung infections have been difficult to determine, but they are known to induce anorexia and increase energy expenditure (for example, by mobilising protein stores in muscle and fat stores in adipose tissue) [98]. There is also evidence of increased protein catabolism in individuals with CF, and that this is associated with a systemic inflammatory response, more severe pulmonary disease and nutritional deficits [44, 99]. Conversely, malabsorption, specific nutritional deficiencies and protein-energy imbalance may result in altered pulmonary defence mechanisms, decreased exercise tolerance and altered pulmonary muscle function [53]. Although the aetiology of malnutrition in CF is unclear, the link with life expectancy highlights the importance of addressing factors that influence nutritional status [9].

Together with respiratory treatments, a preventative approach to malnutrition is viewed as an integral part of the care of individuals with CF (evidence category D). Interventions that enhance nutritional status by addressing the numerous barriers to achieving optimal oral intake are preferred over invasive strategies to treat malnutrition. A meta-analysis of interventions aimed at improving nutritional status found that behavioural interventions were as effective for improving weight as

invasive nutritional support [100] (evidence category B). Optimising health outcomes has the potential to enhance quality of life and reduce the costs of invasive nutrition interventions.

## **2.5 Barriers to optimal intake**

Despite advances in PERT and dietary recommendations over the past two decades, many physiological, psychosocial and environmental factors continue to contribute to sub-optimal intakes, such that elevated energy targets are rarely met [42, 60, 78, 82, 83, 87-91] (evidence category C). Anorexia, dietary preferences, emotional problems, lack of knowledge about nutritional needs, poor adherence to a high fat diet and insufficient dietetic support can have an adverse influence on the oral intake of individuals [60]. Factors associated with reduced appetite include acute and chronic respiratory infection, constipation, distal intestinal obstruction syndrome, abdominal pain, oesophagitis or GOR, fatigue and depression [9]. A dislike for fatty foods, media pressure to eat a healthy low fat, low sugar diet, inappropriate concepts regarding body image, poor use of dietary supplements, behavioural feeding problems, parent-child meal-time interactions and a lack of financial resources can all contribute to reduced food intake [101]. Interventions that minimise the effects of these factors are needed so that short periods of very low intake (with acute respiratory exacerbations) are not superimposed on prolonged poor intakes.

### **2.5.1 Knowledge**

The acquisition of knowledge is important as it is one of the determinants of adherence to treatment [102]. Assessments of CF knowledge indicate that parents and children have significant misconceptions and gaps in knowledge about the disease [103], and about diet and PERT in particular [104, 105] (evidence category C).

There are no comparable data on knowledge in adults with CF. However, it is important to note that it cannot be assumed that adults have adequate knowledge of nutritional management just because their condition is long-standing, particularly if their treatment regimen was managed or supervised closely by their parents for most of their life. In addition, over the lifetime of many of the current adults, there have been substantial changes in standard nutritional advice, including the change in recommendations from a low fat diet to an unrestricted fat diet. Assessment of knowledge is, therefore, an important component of nutritional assessment in the clinical setting (evidence category D).

### **2.5.2 Behaviour**

Much of the CF nutrition literature focuses on mechanisms for providing a high energy, high fat diet with little acknowledgment of the problems faced by individuals with CF and their families in getting the child, adolescent or adult to consume the food and beverages provided. For example, in comparison to non-CF families, parents of young children with CF have noticed more frequent problem meal-time behaviours (excessively long meals, delay of eating by talking, refusing food and spitting food out) [89, 92, 106-108] (evidence category C). It is possible that inappropriate food behaviours and low energy intakes are linked in children with CF [106].

The problem of inadequate oral intakes in children with CF may be compounded by parental reactions to a child's refusal to eat. These parental reactions include increased anxiety, attending to non-eating more than to eating by forced feeding and increased attention through coaxing, physically feeding the child, offering less food, switching to preferred foods rather than risking food refusal or removal from the feeding situation, all of which may inadvertently reinforce non-eating behaviour [109, 110] (evidence category C).

Parental reactions are often fuelled by the emphasis placed by CF health-care providers on optimising children's dietary intake and weight gain [89]. Studies of children with CF exhibiting problematic eating behaviours [109-112] suggest that parents could benefit from participation in specialised behavioural management programs. The training provided could help parents use contingent praise and the setting of limits to reinforce appropriate eating behaviours (see Appendix 5).

Feeding behaviour problems are also common in older children with CF [113] (evidence category B). Thus, nutritional interventions and preventive management should be aimed at children of all ages, not limited to pre-schoolers. Children should participate in their own management and education about CF and nutrition at an age-appropriate level [113] (evidence category D).

Although pre-pubertal children with CF have been found to exhibit similar body esteem to healthy controls [114], adolescents are thought to be at increased risk of disordered eating and/or eating disorders [115]. Disturbed eating behaviours or attitudes, including fear of weight gain despite not being overweight, feelings of being fat, misuse of PERT, binge eating behaviour, or use of exercise to control weight or body shape in adolescents with CF have been reported [116], but no subject met the diagnostic criteria for anorexia nervosa or bulimia nervosa [116, 117] (evidence category C). There is evidence that body weight perception influences nutritional behaviour, and that there are gender differences in this perception [115, 118] (evidence category C).

Of interest is a study that reported that the body image, weight perceptions and eating behaviours of adults with CF were normal despite some problems with body shape perceptions [118] (evidence category B).

### **2.5.3 Complexity of the treatment**

The attainment of optimal oral intakes by individuals with CF is influenced by the complexity of their treatment regimens and that no matter how technologically advanced medical treatments become they will only be effective if they are used [119]. Individuals with CF and their families need to be included in determining, monitoring and modifying therapies, in collaboration with health-care providers, so that perceptions, motivation, skills and factors in the social environment are taken into account [120]. This may be particularly important with dietary intake and PERT in CF as the treatments are numerous and frequent, and have a significant affect on the family's lifestyle [119].

## **2.6 Specialist CF management**

A multidisciplinary approach to care is required for the management of CF [39, 121]. Treatment aims include optimising lung function and nutritional status in order to prevent or reduce the rate of deterioration in clinical condition, whilst maintaining patients' independence and social function [121].

Specialist CF care is best provided by a team of experienced health professionals in a specialist centre [39, 121-123](evidence category C). Specialised services for children and adults with CF should be commissioned separately as some health issues differ with age (evidence category D). Centres should ensure that the transition of services from paediatric to adult care is a positive experience for the individual with CF (evidence category D).

### **2.6.1 Specialist dietetic CF management**

Experienced dietitians have been recognised as a requirement for the "Core CF Team" staffing specialist CF Centres [12, 32, 39, 121]. Specialist centres should provide training programmes with

and for physicians, nurses, physiotherapists, dietitians and social workers providing CF care [12]. As CF is a chronic, life-long condition requiring nutritional management, individuals should be referred to a specialist CF dietitian at diagnosis, and be able to access specialist dietetics services on an ongoing basis for surveillance and management.

The responsibilities of the specialist CF dietitian include the following aspects [39]:

1. Advising and educating individuals with CF and care-givers about the principles of nutritional management. This will include information regarding nutritional requirements at varying stages of health and disease, PERT, vitamin and sodium therapy, assessment of nutritional status and CFRD.
2. Providing age-specific individualised advice, nutritional intervention and nutritional care plans to meet the needs and nutritional and clinical status of individuals with CF. The advice should be appropriately timed and supported by literature resources and aids.
3. Ensuring continuity of care via the same dietitian providing inpatient and outpatient advice, or by maintaining excellent routes of communication.
4. Ensuring that clinical dietetic practice is evidence-based and reflects current research, clinical guidelines and consensus views.
5. Participating in multi-professional audit and research and being available as a nutrition resource person for the training, education, development and support of others involved in CF care.
6. Conducting nutritional surveillance of individuals with CF to ensure regular assessments are conducted, with all aspects of nutrition and gastrointestinal status being reviewed. The frequency and type of assessment will vary with age and clinical status.

### 2.6.2 Staffing requirements

Recommendations for staffing requirements, for the sustained provision of care, have been developed by the Cystic Fibrosis Trust, UK [32, 39]. These staffing requirements have been developed by a number of working groups and committees and have been accepted as representing an overview of expert opinion. The requirements vary depending on the age of the individuals with CF, the severity of their condition and the amount of shared care and community support that a specialist CF centre provides. The numbers may need to be increased where there are a constant higher proportion of very unwell patients with highly complex needs. A health professional requires approximately half or more of their time to be available to work in the area of CF patient care in order to maintain the necessary expertise (evidence category D). These recommendations may need to be adjusted for certain categories of staff in exceptionally large clinics with over 200 patients. The recommended number of whole time equivalent staff required is per every 50 full care patients. Patients receiving shared care would require approximately 50% of the allocation for those receiving full care.

UK recommendations for suggested number of whole time equivalent staff required for every 50 patients on full care [39, 121] (see Appendix 1).

<b>Staff Member</b>	<b>Local Clinic (&lt; 50 patients)</b>	<b>Specialist Paediatric Centre</b>	<b>Specialist Adult Centre</b>
<b>Dietitian</b>	0.4 EFT	0.4 EFT	0.4 EFT

## **Recommendations**

### **1. The management team should include an experienced dietitian to:**

- **undertake a nutritional assessment of losses, requirements and intake**
- **provide education and individualised advice that considers barriers to optimal intake**
- **ensure communication of nutrition issues with the CF team and continuity of patient care, and**
- **conduct nutritional surveillance, audits and research intervention on all individuals with CF.**

**(D)**

### **2. A minimum dietetic service provision of 0.4 equivalent full time (EFT) per 50 CF patients receiving full time care should be allocated (D).**

### 3. Nutritional assessment in CF

#### 3.1 Background

The measures used to assess nutritional status in CF need to be regularly monitored in order to ensure that deteriorations can be detected early, so that malnutrition is prevented or at least minimised [10] (evidence category D). Since no single test provides an accurate measure of nutritional status, a variety of indicators, including height, weight, body composition, dietary and biochemical measurements, are used as a basis for evaluation. Comprehensive annual nutritional assessments are useful for identifying areas of concern and individualising the dietary management of individuals with CF. Additional assessments are required if nutritional or clinical status deteriorates, such as when hospitalised, or there is a risk of deterioration. More frequent monitoring of infants and very young children and individuals who are malnourished, receiving oral or enteral supplementation and/or managing co-morbidities (e.g. CFRD), is required.

#### 3.2 Measurement of height, weight & head circumference

Progressive or episodic deterioration in growth and nutritional status can occur in those with CF [124]. The heavy reliance on assessments of growth only to indicate nutritional status may cause the extent of malnutrition to be largely underestimated as deficits in weight are often not evident until after chronic under-nutrition has developed [53, 125] (evidence category C).

Numerous factors limit the usefulness of measures of height and weight, including:

- variation in the reference standards used to determine growth status
- differences in the criteria used to define growth and malnutrition (weight for height, weight for age, and expressing weight and height as percentiles, percent ideal body weight (%IBW), BMI percentiles and standard deviation or z-scores), and
- variation in the malnutrition cut-off points for each of these indices in different reports.

##### 3.2.1 Techniques & standards for measurement

The equipment and techniques used to obtain anthropometric measurements should conform to accepted practice standards [126, 127], which include:

- taking measurements of a subject dressed in light clothing, without shoes and jumper (age  $\geq 2$  years); or bare (age  $< 2$  years)
- using a stadiometer to measure the standing height of children  $\geq 2$  years and adults; measuring recumbent length in a supine position on a paediatric measuring board of infants and children  $< 2$  years
- weighing toddlers, older children and adults on a platform, electronic chair or beam balance (not bathroom) scale; weighing infants on a paediatric scale in a supine position or weighing the carer and bare infant together as above and then subtracting the carer's weight
- using a flexible non-stretch tape for measuring head circumference in infants  $< 2$  years
- correcting height, weight and head circumference measurements for gestational age in premature infants until 2 years of age
- measurements being obtained by a trained measurer, and
- regular re-calibration of equipment.

### 3.2.2 Frequency of measurement

Table 2 outlines the measurements that should be taken and the frequency of collecting the data. Weight should be measured at every clinic visit, unless visits are very frequent, in which case, minimum fortnightly measurements are suitable for most individuals. Height should be measured three-monthly in children aged over two years, and more frequently in younger infants. Once cessation of growth is demonstrated late in adolescence or early adulthood, then height measurements should be obtained annually. It is important to note that adults may lose height over time due to ageing, osteoporosis or kyphosis.

The genetic potential of individuals aged <18 years should be calculated based on the height of the biological parents. Height and weight should be recorded on centile (growth) charts until 18 years of age, or until transfer to the adult centre, taking into account pubertal delay when interpreting growth data. The growth charts used should be those that are locally available and up-dated whenever suitable new data become available.

Table 2: Suggested minimum frequency for recording anthropometric measurements

Measurement	Infants (0-2 yrs)	Children (2-18 yrs)	Adults (>18 yrs)
Height – supine (length)	1-2 weekly until thriving, then monthly	-	-
Height - standing	-	3 monthly	Annually <sup>2</sup>
Weight	1-2 weekly until thriving, then monthly	Every clinic visit <sup>1</sup>	Every clinic visit <sup>1</sup>
Head circumference	1-2 weekly until thriving, then monthly	-	-
Plot on appropriate growth chart	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	-
% IBW	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	-
BMI	-	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Plot on BMI centile chart	-	<input checked="" type="checkbox"/>	-

<sup>1</sup> Fortnightly if clinic visits are more frequent than this

<sup>2</sup> If growth has ceased; otherwise 3 monthly until cessation of growth is demonstrated (consider that growth may continue up to 20 years in males with CF)

### 3.2.3 Indices of nutritional status

In children, there is no reliable method of accurately estimating malnutrition using height & weight measurements alone. Although the %IBW index has been used as an indicator of nutritional status, it does not detect growth deficits relative to the individual's genetic potential for height (as it is an assessment of weight relative to height) or reflect body composition. It underestimates the severity of malnutrition in children with short stature and overestimates the severity of malnutrition in children with tall stature [128] (evidence category C). In children, plotting of BMI centiles, using the Centres for Disease Control and Prevention (CDC) growth charts (<http://www.cdc.gov/growthcharts>), has been found to be a better indicator of malnutrition than percentage weight for height [128] (evidence category C). For infants (<2 years), there are no reference values for BMI percentiles, so %IBW is used.

The significance of the lower sensitivity of the %IBW index compared to BMI percentiles for detecting malnutrition in children with short stature should not be underestimated, given that short stature is an independent risk factor for poor survival [14]. Also, malnutrition is often underestimated when the %IBW index is used, as individuals who are both short and thin are

classified as normal. Deteriorations in nutritional status will not be detected by the %IBW index if reductions in the velocity of height and weight gain occur at similar rates. Other limitations of %IBW as an indicator of nutritional status include the variation in methodology for calculating the index, wide intra- and inter-individual variation and better correlation of BMI percentile, than %IBW, with pulmonary function [128]. In summary, growth charts, changes over time and BMI percentiles (or %IBW in children <2 years) should be used together to form an anthropometric-based clinical decision regarding the nutritional status of children with CF.

Z-scores are more useful parameters of nutritional status than the above-mentioned indices as height and weight can be separately compared to a reference population, that is similar to the patient group in all aspects except CF. The sensitivity of z-scores compared to %IBW is illustrated in a comparison of growth between children with CF and their siblings. Mean %IBW index values suggested that the two groups were of similar nutritional status, but the age- and gender-adjusted z-score values indicated that the children with CF were shorter and lighter than their siblings [79] (evidence category C). Z-scores are also useful for assessing severely malnourished children, as a quantifiable measure of deficits in nutritional status is obtainable from those whose height, weight and/or BMI is below the 3<sup>rd</sup> percentile. Z-scores also provide a means for monitoring changes in nutritional status, such as with institution of enteral nutrition.

In adults, BMI is frequently used as an indicator of nutritional status. However, the BMI cannot distinguish if deficits or changes are in the fat or fat-free mass compartments, or both [128-130]. It is important to note that if an adult has lost height over time, then caution should be taken to interpret changes in BMI appropriately, and it may be useful to examine changes in total body weight as well as BMI. Weight and BMI can be plotted on long-term charts to assist in the evaluation of changes in nutritional status.

### **3.2.4 Body composition**

#### *Rationale*

Routine, clinical assessments of individuals with CF should include comprehensive, valid and reliable measures of body composition [125]. Evidence from both cross-sectional and longitudinal studies suggest that a decline in lean body mass/fat-free mass may occur as disease severity increases [54, 99, 131-134] (evidence category C). Low stores of fat and/or sub-optimal lean body mass may be responsible for sub-normal growth or underweight in individuals with CF [21, 125, 135, 136] (evidence category C). Monitoring of body composition may enable deteriorations in nutritional status to be detected early, and nutritional interventions to be implemented promptly, before inadequate weight gain, stunting in height, deterioration in pulmonary function and costly invasive nutrition interventions occur [51, 125, 137] (evidence category D).

Deficits in lean body mass (fat-free mass) and fat stores have been reported in both children [62, 125, 138, 139] and adults with CF [44, 99, 140, 141]. When compared with body composition assessments, weight-for-height based indicators of nutritional status appear to underestimate the prevalence of nutritional depletion [125, 138, 142, 143] (evidence category C). The use of measures of body composition should be considered in the evaluation of the nutritional status of all individuals with CF, particularly in those who are malnourished and those undergoing aggressive nutritional support. The frequency of assessments of body composition is dependent on the goals of intervention for the individual and changes in other parameters of nutritional status (evidence category D).

#### *Methods for assessing body composition*

Various assessment techniques have been used to measure body composition in subjects with CF, namely total body potassium, dual-energy X-ray absorptiometry (DXA), total body water and skin

fold thickness measurements. Of the numerous methods available for assessing body composition, some are invasive, expensive and/or not suitable for general use, particularly with children. The methods which rely on a two-component (fat and fat-free mass) body composition model (e.g. skin folds) are less accurate in children as their fat-free mass is continually changing. Multi-component (fat, muscle, bone) models (e.g. DXA and in-vivo neutron activation analysis) provide an accurate and precise assessment of body composition because there are fewer assumptions. However, factors such as cost, limited availability, and exposure to ionising radiation may limit the widespread application of some of these methods. It is advantageous to use the most reliable measures of body composition to assess the nutritional status of individuals with CF if equipment is available and practical to use.

Skin folds may be a viable option for assessing nutritional status if a non-invasive, inexpensive, portable, relatively quick and practical method is preferred. Skin fold thickness measurements are useful for indicating the level of subcutaneous fat and are considered to be an index of stored energy, while girth measurements can be used to estimate muscularity. Skin fold measurements should be taken from multiple sites, including the upper and lower body, trunk and limbs, to account for variations in skin compressibility, skin thickness and tissue patterning with age, within and between individuals [144, 145].

Individual skin fold thickness measurements can be compared with reference population standards and expressed as percentiles or Z-scores. Alternatively, prediction equations have been published for converting skin folds thicknesses into an estimate of fat mass and fat-free mass [146], but caution should be exercised when interpreting the values as there are no CF-specific prediction equations. Measurements undertaken using skin folds do not accurately predict body composition in individuals with CF, when compared with other methods, although correlations are usually high when comparisons are made on a population basis [146-149] (evidence category C).

Future validation of skin folds and girths in individuals with CF, against superior methods such as DXA, may indicate the particular sites that are most representative of nutritional status [125]. The suitability of skin folds for detecting changes in body composition over time has not yet been adequately evaluated in CF [149, 150]. Monitoring of measures of body composition, by graphing serial z-scores of the anthropometric measures or by using a computer program to display comparisons between different occasions, could be useful for assessing the effects of various interventions in both acute and chronic situations (evidence category D).

### ***3.3 Dietary intake***

#### **3.3.1 Methods for assessment**

There are numerous methods available for assessing dietary intakes, such as weighed intake records, dietary record diaries, food frequency questionnaires, 24 hour recalls and diet histories. The accuracy of assessments of dietary intake is limited by methodological problems [93]. These problems are compounded in children due to the difficulties they may have in remembering their intake and their cognitive ability to complete dietary records [151]. The technique chosen largely depends on the ability of the target group to comply with the method, the resources and time available, the purpose for collecting the information and the specific nutrients of interest. Diet histories, 24-hour dietary recalls and 3 to 5 day prospective dietary records are the techniques most commonly used in the clinical setting. There is minimal information in the literature regarding what tools are most advantageous for assessing dietary intake.

### 3.3.2 Frequency

A thorough dietary assessment should be conducted at least annually (evidence category D). More frequent assessment of dietary intake is warranted in very young children; in those who are malnourished, have co-morbidities or are at risk of deterioration of nutritional status; and to assess the effects of intervention.

In addition to periodic review as an outpatient by a dietitian with expertise in CF, the dietary intake of all inpatients should be assessed. Information collected will be useful for optimising the management of current nutritional issues, including those related to the reason for hospitalisation and those identified at the most recent outpatient visit. A revised nutrition management plan should be implemented during the admission and upon discharge (evidence category D).

### 3.3.3 Scope

Table 3 indicates the key areas to review during a dietary assessment. Dietary intake data is useful for assessing the adequacy of an individual's intake, including energy and fat intake, use of PERT, vitamin and mineral supplements and oral and enteral nutrition supplements, determining where energy intake or density may be increased, deciding how enzyme use may be optimised and for reviewing food-related knowledge, attitude and behaviours (family dynamics, eating patterns and recent stressors) [152]. Complementary or alternative medications should be assessed by the dietitian, pharmacist and/or physician in order to determine safety and efficacy [153]. Dietary records are also used in faecal fat balance studies to assess fat intake (see section 5.2).

Table 3: Dietary factors to assess in individuals with CF

<b>Key area of assessment</b>	<b>Purpose</b>
Energy intake	Energy balance & affect on weight
Fat intake	Energy density, PERT adequacy
Food preferences & variety Meal pattern & behaviours Knowledge & attitudes about nutrition, including body image	Adequacy of micronutrient intake Fibre intake Target areas for change
PERT: dosage, adherence & gastrointestinal symptoms	Adequacy of PERT regimen
Supplements: vitamins & minerals, oral & enteral nutritional supplements	Adequacy of micronutrient intake Contribution to energy & nutrient intakes
Sodium & fluid intake	Hydration & sodium status
Nutrition-related complementary or alternative therapies	Contribution to micro- & macronutrient intake

## 3.4 Biochemical assessment

### 3.4.1 Methods & frequency

Biochemical tests provide important information about the nutritional status of individuals with CF. Table 4 details the tests that are suggested, and the suggested frequency, for assessing parameters such as vitamin and mineral status. All individuals should be assessed at diagnosis and thereafter on a routine basis and more frequently if there is a risk of deterioration in nutritional status or when treatment protocols change.

Table 4: Biochemical monitoring of nutritional status in individuals with CF

Parameter	Test	Target group and frequency	Notes
Fat-soluble vitamins A,D,E,K	Retinol and retinol binding protein; 25-hydroxyvitamin D; $\alpha$ -tocopherol; prothrombin time	All patients At diagnosis Annually in stable patients More frequently if monitoring a deficiency, evaluating efficacy of treatment or assessing individuals with liver disease or intestinal resections	Low serum levels of vitamins A and E have also been observed in those individuals with pancreatic sufficiency [154] (evidence category C).  The levels of all fat-soluble vitamins should be routinely tested at the same time to aid interpretation of abnormal findings that may be due to factors such as adherence or malabsorption.  Vitamin A levels should be measured when subjects are clinically stable [155] (evidence category C).  The season should be taken into account when interpreting levels of vitamin D, due to seasonal variation.  Usefulness of the alternative test for vitamin E, the ratio of vitamin E:total lipid [11], which corrects for plasma lipid levels has not been established in CF [154].  Vitamin K status can be assessed using the PIVKA II test [8], but it is not routinely available in the Australasian clinical setting.

<b>Parameter</b>	<b>Test</b>	<b>Target group and frequency</b>	<b>Notes</b>
Glucose metabolism: screening for CFRD	Oral glucose tolerance test (OGTT)  or  Serial monitoring of fasting and two hour post prandial blood glucose measures.	Either: Annually for individuals >10 yrs  Or  selectively in individuals >10 yrs and in those experiencing poor growth, difficulty maintaining weight or an unexplained decline in respiratory status. (Practice varies in Australia)  Serial monitoring is also recommended in the following situations: during infections, steroid treatment, before, during and after enteral feeding, in pregnancy.	OGTT is considered to be the most sensitive method for identifying CFRD [156] (evidence category C), but may not be practical to undertake in all patients. OGTTs should be performed when patients are clinically stable  In addition to OGTT diagnosis, elevated fasting or random plasma glucose levels with abnormal serial glucose monitoring, symptoms of hyperglycaemia or elevated HbA1c would also indicate CF related diabetes. It should be remembered that impaired glucose tolerance (IGT)/CFRD can be transient and may resolve albeit temporarily. Close monitoring of patients with such features should follow [157] (evidence category D).  HbA1c is not sufficiently sensitive for detecting CFRD, possibly because hyperglycaemia is transient, or mild; or because red blood cell turnover is elevated due to chronic inflammation in CF [158, 159] (evidence category B).
Glucose metabolism: monitoring at-risk patients	Pre- and two hours post-prandially	During infection, steroid treatment and/or enteral feeding.	Transient hyperglycaemia may require treatment with insulin.
Glucose metabolism: monitoring established CFRD	Regular home blood glucose monitoring	As advised individually.	
	HbA1c	3-6 monthly	

Parameter	Test	Target group and frequency	Notes
Iron studies	Serum iron; Transferrin; Ferritin  Soluble transferrin receptor	All patients, minimum yearly  More frequently in individuals with known iron deficiency, who are receiving treatment to increase levels or have increased iron losses (e.g. haemoptysis)  In patients with raised C-reactive protein (CRP) and ferritin levels <200ng/ml.	Transferrin saturation may overestimate iron deficiency. Ferritin may underestimate iron deficiency. Soluble transferrin receptor may be more useful for detecting iron deficiency as it is not affected by the acute phase response [160] (evidence category C).  Include measurement of CRP level to aid interpretation of iron studies.
Zinc	Serum zinc	In conjunction with assessment of vitamin A status in individuals with low levels that are unresponsive to supplementation.	Zinc deficiency has been suggested as a possible contributing factor to vitamin A deficiency [11]. Zinc is required for the release of vitamin A and retinol binding protein from the liver [161].
Liver function tests	Liver enzymes; total protein and albumin	All patients  Annually  More frequently in individuals: - with known liver disease, - with acute or chronic elevation of enzymes, or - on medication associated with elevated enzymes.	Reduced albumin levels may be a consequence of, or reflect, inflammation, infection and/or liver disease rather than nutritional status.
Renal function/ electrolytes	Urea, creatinine, sodium, potassium, chloride, osmolarity	All patients  Annually  More frequently: - during hospital admissions - if dehydrated - if has CFRD, or -if has renal impairment.	Serum sodium alone is an insensitive marker of sodium depletion and should be interpreted in conjunction with serum chloride levels and clinical presentation.

### **3.5 Other assessment factors**

Nutritional assessment in individuals with CF should also include:

- screening for, and treatment of, nutrition-related co-morbidities, including pancreatic insufficiency, CFRD, GOR, BMD and liver disease (see sections 6-8).
- investigation of nutritionally-related medications
- a review of bowel habits and function, and
- information regarding relevant lifestyle factors, including exercise and physical activity.

### **Recommendations**

- 1. Periodic nutritional assessments should encompass a collation of anthropometric, dietary, biochemical and relevant clinical data. Deterioration in parameters of nutritional status should be detected early, before growth and pulmonary function are compromised (C).**
- 2. Height, weight and head circumference (in those aged <2 years) should be measured regularly (see Table 2). Measurements for individuals with CF aged <20 years should be plotted on appropriate growth charts (D).**
- 3. Anthropometric techniques should conform to accepted practice standards (D).**
- 4. Age appropriate indices should be calculated:**
  - percentiles for height and weight and %IBW in infants aged <2 years
  - percentiles for height, weight and BMI in individuals aged 2-18 years, and
  - BMI in adults (D).
- 5. Body composition assessments should be considered in individuals with CF, especially those who are underweight (<5<sup>th</sup> % ile for BMI in children and BMI <20 kg/m<sup>2</sup> in adults) and in those undergoing aggressive nutrition support. DXA; in vivo neutron activation analysis or total body potassium counting are the preferred methods for body composition assessment, but if unavailable, skin folds and limb circumference measurements are useful (D).**
- 6. Annual, detailed dietary assessments should be undertaken in individuals with CF, and more frequently (e.g. three monthly) in those who are admitted to hospital, malnourished, very young and/or have CF co-morbidities (D).**
- 7. Periodic biochemical assessments of nutritional status should be undertaken (see Table 4) (D).**

## **4. Nutritional requirements in CF**

### **4.1 Background**

The nutritional requirements of individuals with CF are difficult to define due to the variable expression of the disease, clinical state and physical activity level. In general, a diet high in energy, fat and protein is required to achieve optimal nutritional status. Following is a summary of the nutritional requirements of individuals with CF based on consensus documents produced by health professionals from the United Kingdom (UK), Europe and the United States of America (USA) [8, 10, 11, 162]. Although the RDIs for the general population are used as a benchmark for CF dietary recommendations, this practice is limited by the origins of RDIs and variations between countries. In brief, RDIs are based on the general healthy population and are set at levels of intake that are considered to be adequate to meet the known nutritional needs (with a safety margin) of most healthy individuals so that deficiencies and diseases are prevented.

The recommendations that follow are useful as a general guide for the management of CF, but the nutritional status of each individual with CF should be closely monitored in order to determine specific needs. Routine, comprehensive monitoring is essential as nutritional requirements can vary widely between, and over time, within individuals with CF.

### **4.2 Macronutrients**

#### **4.2.1 Energy**

Although only a crude estimate, it is often suggested that individuals with CF require between 120 and 150% of the normal RDI of energy for age and gender to compensate for elevated expenditure and losses from malabsorption [8, 10, 85, 163]. CF specific prediction equations have been proposed, but found to yield inaccurate estimates of energy requirements [164, 165], most likely due to wide inter-individual variation in REE, activity levels and reported intake (evidence category B) (see section 2). Ideally, individual assessments of metabolic needs should be conducted [60], but this is difficult as equipment and expertise for indirect calorimetry is not routinely available in CF clinics.

It is likely that energy requirements vary widely amongst individuals, as a range of intakes from 110-200% RDI for energy have been observed to be associated with improved weight gain (V. Stallings, personal communication, 2005). Therefore, individual estimation of energy requirement is required, taking into account nutritional status, growth pattern, current dietary intake, degree of fat malabsorption, clinical status (including pulmonary function), level of activity; and incorporating additional requirements for nutritional repletion, weight gain and/or catch-up growth, if necessary (evidence category D). It is possible that energy requirements are not elevated in individuals with close to normal lung function ( $>80\%$  predicted forced expiratory volume in one second (FEV<sub>1</sub>)) and in the absence of oxygen dependence or acute respiratory infections [166] (evidence category B). Thus, the recommendation for energy intake between 120 and 150% RDI for individuals with CF should be considered as a guide only.

#### **4.2.2 Fat**

In CF, fat intake should be unrestricted, unless the individual is overweight, as a diet high in fat is less bulky and more likely to be achieved than a low fat diet of similar energy value. For individuals with high energy requirement, the diet should be as high in fat as possible within the limits of individual tolerance. The energy cost of converting dietary fat to body fat is minimal compared to the conversion of dietary protein and carbohydrate to body fat.

Nutrition guidelines have traditionally suggested that fat should provide 40% of the daily energy needs of individuals with CF if total energy intakes of more than 125% of the RDI are to be achieved [167, 168]. An alternative, more practical recommendation for individuals with CF aged greater than 5 years is to consume >100 g fat/day [78] (evidence category C). The fat gram target is useful for:

- self-monitoring adherence to dietary goals
- screening for individuals with sub-optimal energy intakes
- education regarding ongoing dietary intake, and
- for rationalising PERT intake.

In practice, the fat content of the usual diet can be increased for the individual with CF, for example by fortifying meals with margarine and cream, and by providing additional nutritious high fat foods (such as cheese, meats and milk-based desserts) and milk drinks. At this point in time, there is insufficient evidence to recommend one specific fat subtype for people with CF.

Mean serum cholesterol levels in a group of adults with CF were significantly lower than controls despite higher dietary intakes of fat, and no CF subjects in this study had a serum cholesterol of greater than 5.5mmol/L [169]. These findings, together with the observation of a low prevalence of other risk factors for heart disease such as smoking and obesity, should assist with reassuring individuals with CF who require high fat diets that they are unlikely to be exposing themselves to an elevated risk of heart disease by including saturated fats in the diet (evidence category D). However, in selected individuals, such as those who are overweight or those who do not require high fat diets to achieve adequate energy intake, advice that is consistent with general population recommendations for fat subtypes may be more appropriate (evidence category D).

#### **4.2.3. Protein**

Protein requirements are thought to be elevated in individuals with CF, but there is no specific recommendation for intake. Intakes of individuals with CF are often well in excess of recommendations for the normal population [84] (i.e. 0.9-1 g protein/kg body weight for those aged 1-18 years; 0.75g protein/kg body weight for adults [170]).

Factors that may be responsible for increasing protein requirements in individuals with CF include malabsorption, an excessive loss of nitrogen in the faeces and sputum and the possibility of altered protein metabolism [171].

It is likely that protein needs will be met if a high energy diet is attained and protein constitutes 15% of the energy intake [171] (evidence category C), as protein intake has been observed to increase as energy intake increases [172].

#### **4.2.4 Carbohydrate**

Carbohydrate intake should be as high as required to meet energy requirements, in conjunction with a high fat diet. If CFRD develops, then modification of the distribution of carbohydrate during the day may be required (see section 7).

#### **4.2.5 Fibre**

Extremes of fibre intake are not thought to be suitable for individuals with CF. A very low fibre intake (<10 g/day) can contribute to constipation and abdominal pain in an individual with CF [173] (evidence category C). A diet high in fibre is not universally recommended in CF as food and hence energy intake may be limited by the high satiety value of this nutrient [152]. Thus, a moderate fibre intake (e.g. 10-30g/day for adults) may be suitable given that it does not appear to be associated with gastrointestinal symptoms [174] (evidence category B).

### **4.3 Vitamins**

#### **4.3.1 Prevalence of deficiency**

Deficiencies of fat-soluble vitamins A, D, E and K have been repeatedly demonstrated in individuals with CF, particularly in those with pancreatic insufficiency [17, 18] (evidence category B). Even infants less than three months old have been observed to have biochemical deficiencies of vitamins A, D and E [175, 176] (evidence category B). Biochemical deficiencies have been shown to be associated with poorer clinical status in individuals with CF [177] (evidence category B). In contrast, significant deficiencies of water-soluble vitamins are not common [18] (evidence category C).

#### **4.3.2 Factors contributing to deficiency**

Factors that may contribute to deficiency states of fat-soluble vitamins in individuals with CF include:

- inadequate intake
- malabsorption possibly due to suboptimal PERT
- malabsorption due to residual or incomplete bile salt absorption
- poor clinical status and reduced lung function
- increased utilisation and reduced bioavailability
- liver disease
- bowel resection
- late diagnosis of CF, and
- poor adherence to or inappropriate supplementation regimens [8, 10, 11, 58, 178-180].

#### **4.3.3 Monitoring of vitamin status**

See section 3.4 and Table 4 for further information on biochemical monitoring of vitamin status in individuals with CF.

Monitoring of vitamin levels should be completed annually in children and adults to determine vitamin status and the efficacy of supplementation [175] (evidence category B).

Numerous factors can affect biochemical levels of vitamins, including seasonal variations and the factors that contribute to deficiency states (see section 4.3.2). Tests that assess tissue stores and function of vitamins are more accurate than blood levels, but are invasive and may not be available in all CF centres [11]. For example, as retinol is stored in the liver, a liver biopsy is required to examine vitamin A storage levels. Further research may be able to determine whether, and in what situations, more invasive assessments of vitamin status are warranted in individuals with CF [175] (evidence category B).

It is suggested that vitamin status be monitored during periods of clinical stability [8]; that the season of assessment be noted for vitamin D. Appropriate reference ranges should be used to determine biochemical status. The clinical significance of biochemical deficiencies in the absence of overt signs of clinical deficiency is unclear. Biochemical assessment of vitamin status appears to be most useful for identifying individuals with CF with normal, extremely low or very high levels (when compared to appropriate reference ranges). Vitamin supplementation can then commence and regimens adjusted until appropriate levels are achieved.

Numerous studies have demonstrated repeated presence of biochemical deficiencies despite routine supplementation [175, 181] (evidence category C). Thus, periodic monitoring and assessments of adherence should be conducted until appropriate levels are achieved. Interpretation of slightly low or high levels is more difficult than interpretation of frankly low or high levels in terms of determining if a change in supplementation is necessary.

#### 4.3.4 Supplementation

Vitamin dosage recommendations vary significantly within and between CF centres, both nationally and internationally, as is evident in the European, UK and USA Guidelines [8, 10, 11]. This variability is due to the lack of strong evidence regarding vitamin dosing in individuals with CF and also due to local variations in available preparations, prescribing and dispensing systems.

Some CF centres recommend routine prophylactic vitamin supplementation, while others supplement only when a deficiency state is detected. The cost of supplementation in Australia and New Zealand is another factor influencing practice. When vitamin supplements are not routinely available on prescription, unless a deficiency state exists, the patient or family will generally incur the cost of prophylactic treatment.

Table 5 provides recommended starting doses for each of the fat-soluble vitamins. In the absence of conclusive evidence, these starting doses are based on international recommendations for vitamin supplementation [8, 10, 11], the preparations commonly available in Australia and New Zealand and known upper levels for avoiding toxicity.

Table 5: Recommended starting doses for vitamin supplementation in individuals with CF (evidence category D)

Age	Vitamin A (IU)	Vitamin D (IU)	Vitamin E (IU)	Vitamin K (µg)
0-12 mths	1500-2000	400-1000	40-80	150-500
1-3 yr	1500-2500	400-1000	50-150	150-500
4-7 yrs	2500-5000	400-1000	150-300	300-500
8-18 yrs	2500-5000	400-1000	150-500	300-500
Adults	2500-5000	400-1000	150-500	300-500

Vitamin A: 1 mg retinol = 3.3 IU Vitamin D: 1 µg = 40IU ergocalciferol or cholecalciferol

Vitamin E: 1 mg RRR- $\alpha$ -tocopherol = 1.5 IU, 1 mg all-rac- $\alpha$ -tocopherol = 1 IU

Factors that should determine the type of preparation to be prescribed include the vitamin that requires supplementation, adherence, cost and accessibility. Standard multivitamin preparations are often not complete sources of fat soluble vitamins or high enough levels for CF requirements. A CF-specific multivitamin preparation, VitABDECK®, is available in Australia (see Table 6). Fat-soluble vitamin preparations should be taken in conjunction with PERT to enhance absorption, however the fat soluble vitamins in VitABDECK® are water miscible and may not require PERT.

Table 6: Composition of VitABDECK®

VitABDECK®	Vitamin A	Vitamin D	Vitamin E	Vitamin K
Per capsule	2500 IU retinol + 3 mg β-Carotene	440 IU	150 IU	150 ug
Per ml of liquid (Usual dose 3 ml)	665 IU retinol +1.2mg β-Carotene	150 IU	19 IU	50 ug

\*Note that VitABDECK® also contains vitamins B and C and zinc

The use of individual fat soluble vitamin supplements is appropriate if VitABDECK® is not available or is not suitable. For example, when supplementation of all the fat-soluble vitamins is not required or the dosage required differs from that available in the preparation. See Table 7 for doses of vitamins commonly available in Australia and NZ.

Table 7: Doses of vitamins A, D & E in preparations commonly available in Australia & New Zealand

Vitamin	Form	Dose
Vitamin A	liquid	2 200 IU/ml <sup>1</sup>
	capsule/tablet	5 000 IU
Vitamin D	capsule	1 000 IU
Vitamin E	liquid	100-150 IU/ml
	capsule/tablet	100, 250, 500 IU

<sup>1</sup> in combination with vitamin E

#### 4.3.5 Vitamin A

##### *Role, sources & deficiency*

Vitamin A is an essential nutrient for epithelial cell maintenance and repair. Dietary vitamin A (retinol or retinol esters) is found in eggs, fish, the fat of dairy products and vitamin A fortified margarine. β- and α-carotene can act as precursors for the synthesis of vitamin A. The dietary carotenoid, β-carotene, is found in red, orange, yellow and leafy green vegetables and red and orange fruit. Carotenoids are thought to function as antioxidants, inhibiting the oxidation of membrane lipids during an infection.

Deficiency of vitamin A may cause night blindness, conjunctival and corneal xerosis, dry thickened skin and abnormalities of bronchial mucosal epithelialisation [182], [101], [177], [183].

Vitamin A deficiency in individuals with CF appears to be multifactorial. Low retinol levels have been observed during periods of infection and inflammation [155, 184] therefore assessment should occur during periods of clinical stability, rather than during acute exacerbation of lung disease (evidence category B). Low levels may also be a consequence of low levels of retinol binding protein, which transports vitamin A from the liver to tissues, or low levels of zinc, which is required for the release of vitamin A and retinol binding protein from liver stores [11, 177] (evidence category B). Measurement of retinol binding protein and zinc at the same time may assist with the interpretation of low vitamin A levels [11].

### *Monitoring & supplementation*

Internationally, there is lack of consensus for optimum serum levels of vitamin A in individuals with CF, therefore reference ranges for the general population are often used. If the level of serum vitamin A is found to be below the laboratory reference range, then supplementation should commence at an age appropriate dose as outlined in Table 5. If serum levels do not increase appropriately with increased dosing then further investigation is warranted.

The upper limit of dosing for vitamin A has not been established, but a dose of 20 000 IU/day has been suggested if retinol binding protein is low [10]. Caution with supplementation is necessary as individuals with CF, in comparison to healthy controls, can have an increased hepatic vitamin A reserve which could lead to hypervitaminosis if doses are excessive [101, 183] (evidence category D).

### *Pregnancy*

Vitamin A supplementation during pregnancy should be carefully considered [10] (evidence category D) ( See section 9).

## **4.3.6 Vitamin D**

### *Role, sources & deficiency*

Vitamin D plays an essential role in regulation of calcium homeostasis and therefore bone mineralisation. The major source of vitamin D in Australia is exposure to sunlight, while small amounts are derived from dietary sources, such as cod liver oil, oily fish and fortified foods (although fortification is not routine in Australia).

Deficiency states are thought to be mostly due to decreased exposure to sunlight in more sedentary individuals and those living in countries where there is limited sunshine [17, 185]. Low levels of vitamin D have been demonstrated throughout all age groups in the CF population but mean levels vary across populations due to geographic and sunlight exposure differences [42, 45, 175, 186] (evidence category B). Deficiency has been related to decreased BMD and osteopaenia in adults with CF [42, 187] (see section 8).

### *Monitoring & supplementation*

There is no universal consensus regarding optimum serum 25-hydroxyvitamin D (25-hydroxyvitamin D) levels in individuals with CF. It should be noted that assays of 25-hydroxyvitamin D vary between laboratories [188] (evidence category B). In the absence of CF-specific evidence, it may be appropriate to define vitamin D insufficiency using the same level as for the general population, being <50 nmol/L of vitamin D [189-191] (evidence category C). As serum levels of 25-hydroxyvitamin D are inversely correlated with serum levels of parathyroid hormone, elevated parathyroid hormone levels have been used to assist with defining insufficient vitamin D levels. Season of measurement should always be considered when interpreting results [192], as vitamin D levels have been observed to be higher in summer than winter [42, 186] (evidence category C).

Due to the large variation in climatic conditions and sunlight across Australia and New Zealand, Vitamin D supplementation practices vary between and within centres. Use of supplements, and supplement doses should be based on results from an assessment of vitamin D status and clinical

aspects, including health status, dietary intake and lifestyle [193] (evidence category C). It is possible that supplementation of vitamin D does not need to be increased if serum 25-hydroxyvitamin D levels are >80 nmol/L as supplementation had minimal effect on serum levels that were at this level in a group of early post-menopausal women [194] (evidence category C).

Most locally available preparations (solely vitamin D or as part of a mixed preparation) contain ergocalciferol (25-hydroxyvitamin D<sub>2</sub>) or cholecalciferol (25-hydroxyvitamin D<sub>3</sub>). Table 5 details suggested starting doses. Further investigation is warranted if a supplementation dose of 5 000 IU/day does not normalise serum levels. Possible reasons for non-response to vitamin D supplementation include poor adherence, malabsorption (secondary to incorrect administration, non-adherence to PERT and liver disease) and poor activation of vitamin D to the active form 1,25 dihydroxyvitamin D (due to renal disease).

Additional monitoring of serum levels is warranted in individuals with CF who are receiving high dose supplementation. Vitamin D toxicity in the normal population has been associated with serum 25-hydroxyvitamin D levels >200 nmol/L [188] (evidence category B) and results in hypercalcaemia and/or elevated urinary calcium.

#### **4.3.7 Vitamin E**

##### *Role, sources & deficiency*

Vitamin E acts as an antioxidant protecting against oxidation of polyunsaturated fatty acids, particularly in lipoproteins and cellular membranes. The major physiological form of vitamin E is  $\alpha$ -tocopherol. The main sources of vitamin E in the diet are vegetable oils, nuts, seeds, wholegrain breads and cereals, green leafy vegetables, fish, seafood, meat and poultry.

Vitamin E deficiency is common in individuals with CF and severe deficiency has been associated with haemolytic anaemia in infants [195] (evidence category C) and ataxia, neuromuscular degeneration or compromised cognitive function in older patients [8, 50] (evidence category B).

##### *Monitoring & supplementation*

The serum level of  $\alpha$ -tocopherol is the most common method used to assess vitamin E status. An alternative test is the ratio of vitamin E:total lipid which corrects for plasma lipid levels of vitamin E. The ratio provides a more accurate reflection of vitamin E status in hyperlipidaemic states, but its use in individuals with CF has not been established, possibly because the more common lipid abnormality in CF is hypolipidaemia [154].

Recommendations regarding routine vitamin E supplementation doses vary internationally. The major form used in preparations is  $\alpha$ -tocopherol and either water- or fat-soluble forms are suitable for use [196] (evidence category B). A safe upper limit for vitamin E supplementation has not been determined for individuals with CF, but in adults without CF the level is thought to be 1600 IU [11, 197].

#### **4.3.8 Vitamin K**

##### *Role, sources & deficiency*

Vitamin K is an essential co-factor for activation of prothrombin and is involved in blood coagulation, osteocalcin, calcium balance and bone mineralisation. Dietary sources of vitamin K include green leafy vegetables, margarine, plant oils, liver and fermented food products.

The risk factors for deficiency are the same as those for all fat-soluble vitamins, but also include frequent antibiotic treatment in individuals with CF [198] (evidence category B), which results in a reduction of intestinal microflora that have the capacity to produce vitamin K. Clinical deficiency of vitamin K is considered to be rare in CF, however subclinical deficiencies have been shown in more than 80% of pancreatic insufficient children and in all patients with significant liver disease [199, 200] (evidence category B). More recently, suboptimal vitamin K status on the basis of low serum vitamin K and prothrombin produced in vitamin K absence (PIVKA II) was demonstrated in 70% of children with CF [201].

#### *Monitoring & supplementation*

Plasma levels of vitamin K are an unreliable measure of status [8, 11]. Prothrombin levels can be indicative of severe vitamin K deficiency, but are rarely abnormal, even in advanced liver disease [11, 199] (evidence category B). Subclinical deficiencies have been demonstrated using PIVKA-II levels but this more sensitive test is not readily available [199] (evidence category B).

Prophylactic supplementation of vitamin K is essential for all individuals with liver disease and for those who are on frequent antibiotic regimes [8]. The demonstration of subclinical deficiencies of vitamin K suggests that prophylactic supplementation of all patients with pancreatic insufficiency may be warranted.

Internationally, there is a lack of consensus regarding supplementation dosages of vitamin K. Subclinical levels of vitamin K were not corrected by weekly five mg doses [202] (evidence category B). Thus, it may be necessary to administer daily doses of vitamin K in order to accommodate metabolic turnover time [11]. Toxicity of Vitamin K has not been reported in individuals with CF.

#### **4.3.9 Water-soluble vitamins**

Significant deficiencies of water-soluble vitamins have rarely been reported in CF until recently. Eighty percent of the children who presented at a CF clinic with angular stomatitis were found to have biochemical evidence of B-group vitamin deficiency [203]. Supplementation of water-soluble vitamins is required if dietary intake is inadequate and/or there is evidence of deficiency, however, optimal dosage levels have not been defined. Monthly parenteral Vitamin B<sub>12</sub> supplementation is required if the terminal ileum has been resected [58].

#### **4.4 Minerals**

See section 3.4 for further information on biochemical monitoring of mineral status in individuals with CF, including Table 4.

##### **4.4.1 Sodium and fluids**

#### *Deficiency*

All individuals with CF are at risk of increased sweat losses of sodium and chloride with exercise or exposure to high temperatures [204]. Infants with CF are particularly at risk of salt depletion due to low levels of sodium in breast milk and substitutes. Sodium chloride deficiency is characterised by hyponatremia, decreased serum osmolarity, decreased appetite, nausea, vomiting, muscle cramps, deposits of sodium chloride crystals on the skin, fatigue, poor concentration and headaches [205] (evidence category C). Hyponatraemic dehydration may have clinical implications, by contributing to thicker and more difficult to expectorate sputum, and may also lead to distal intestinal obstruction syndrome (DIOS) [206].

## *Monitoring*

Serum electrolytes and spot urine analysis are useful for interpreting symptoms of sodium deficiency, especially in infants, during acute illness and in hot climates. There is a lack of consensus regarding the usefulness of these investigations on a routine basis because they are not reflective of sodium levels during periods of exercise and heat stress [11] (evidence category D).

## *Supplementation*

Include an individualised assessment of and counselling regarding the sodium content of the diet, including added salt and fluids containing sodium, supplement dosage, serum levels (when available), hydration status, activity level, illness and climate. Additional sodium supplementation may be needed:

- by infants, as requirements are increased during rapid growth and due to their large body surface area [10].
- during periods of illness, due to reduced intake associated with poor appetite and increased losses if febrile
- when regular dietary intake decreases and is replaced by oral fluid supplements or enteral tube feeds, which have a low sodium content
- before undertaking additional strenuous work or physical activity, and
- when holidaying, living or working in hot or humid conditions.

There is a lack of evidence and international consensus regarding the need for sodium replacement and dosage in individuals with CF. The dosage of sodium recommended is often based on an individual's symptoms, dietary intake, climatic conditions, humidity and exercise or activity level. It is important to note the wide variation in climate across regions of Australia and New Zealand. In many areas of Australia (particularly Queensland, Northern Territory and Western Australia) anecdotal evidence suggests that sodium and fluid requirements are raised year round.

Recommended doses of sodium range from:

- 500 to 1000 mg/day for infants
- up to 4000 mg/day for children, and
- 6000 mg/day for adolescents and adults.

Sodium requirements may exceed these levels during extreme weather conditions or excessive exercise. Monitor individual signs and symptoms to determine the level of sodium supplementation required.

Sodium intake may be increased by:

- adding salt to food and cooking (1 tsp = 2000 mg sodium)
- including foods high in salt such as salted nuts, crisps, cheese and vegemite
- drinking fluids high in sodium, as follows:
  - rehydration solutions such as Glucolyte® or Gastrolyte® (360 mg sodium per sachet)
  - commercial sports drinks such as Gatorade® (280 mg sodium per 600 ml bottle)
  - home-made sports drinks such as ¼ teaspoon salt added to 500 ml water/cordial (500 mg sodium)
  - administering salt supplements (1 tablet = 240 mg sodium)
  - if traditional salt tablets are not tolerated or available, self prepared salt capsules can be prepared by adding ¼ to ½ teaspoon table salt to empty gel capsules available from commercial pharmacies
  - for infants, administer additional NaCl by mixing the powder in apple puree (amounts depend on current feeding regimen, local climate and centre practices, but can be up to 300 mg of NaCl per day)

Ingestion of high concentrations of sodium at any one time may result in nausea and vomiting. Practical strategies to overcome these symptoms include gradually increasing sodium intake over time, trialling salt tablets with food and spreading sodium intake over the day.

Individuals with CF should be educated regarding the necessity for additional fluid with sodium supplementation. Level of thirst should not be relied on to estimate fluid requirements in times of likely dehydration because a low serum osmolality, associated with depletion of sodium and chloride, may diminish the thirst drive [204] (evidence category C). Minimum fluid requirements will be higher than that needed by the normal population, with planned increases during periods of illness, infection and sweating.

#### 4.4.2 Iron

Iron deficiency is common in individuals with CF and may be related to multiple factors including inadequate dietary intake, malabsorption, haemoptysis, gastro-oesophageal reflux (blood loss, H<sub>2</sub> blockers and antacids), short bowel syndrome and bacterial bowel overgrowth, liver and renal complications, chronic infection, and excessive losses in sputum [207] (evidence category C). It has been suggested that the prevalence of iron deficiency is high in people with CF and pseudomonas infection [207]. The prevalence of iron deficiency in people with CF has been reported to be 32-62% [208-210].

The interpretation of biochemical test results for iron status is complicated by chronic inflammation. Usually, in iron deficiency states, serum transferrin is high and ferritin is low. However ferritin and transferrin are acute phase reactants and will be raised in chronically infected individuals (e.g. as indicated by a raised CRP), with ferritin often appearing within normal limits when iron stores are in fact low.

The soluble transferrin receptor level may more accurately reflect iron status but this test is not as readily available. A high soluble transferrin receptor level indicates iron deficiency and is not affected by the inflammatory state. The soluble transferrin receptor level can also be increased if red blood cell turnover is increased (haemolytic anaemia).

It is important to check iron studies during periods of clinical stability and to perform a CRP concurrently (evidence category D). Where serum iron is low and:

- (i) ferritin < 20ng/ml, this indicates iron deficiency anaemia and iron supplementation should be commenced
- (ii) ferritin >200ng/ml, anaemia of chronic disease is more likely and iron supplementation is not warranted
- (iii) ferritin between 20-200ng/ml, iron deficiency anaemia could be masked by anaemia of chronic disease and the management appropriate is less clear.

Where the CRP is raised, a soluble transferrin receptor level should be requested and if this is raised, iron supplementation should be commenced (evidence category D). If this test is not available, another option is to commence iron supplementation and monitor haemoglobin levels (evidence category D). Where iron supplementation is able to manage iron deficiency anaemia, an increase in haemoglobin by 1-2g/dl within 4 wks is expected (evidence category D).

The mean cell volume, or MCV, is increased in markedly iron deficient states but can be normal even if iron stores are moderately depleted. Ferritin is better at identifying iron deficient states before MCV is reduced.

Assistance from a haematologist may be beneficial in interpretation of iron studies.

Iron supplementation may produce side effects including gut irritation, discomfort and constipation. Where this occurs, liquid iron or IV iron may be considered (evidence category D). After starting supplementation, levels should be monitored at least six monthly (evidence category D).

#### **4.4.3 Calcium**

##### *Deficiency*

Over the past two decades, the high prevalence of low BMD amongst adolescence and adults with CF has become apparent (see section 8). The aetiology of bone disease in CF is multifactorial, with poor nutritional status, infection and inflammation, glucocorticoid use, hormonal status and limited weight bearing activities being associated with reduced BMD [192] (evidence category C). Calcium is the major mineral of bone and sufficient calcium is required as a substrate for bone mineralisation [211] (evidence category C). Although individuals with CF are thought to be at risk of calcium deficiency [212] (evidence category C), there is a lack of research assessing the efficacy of calcium supplementation in this group. In the absence of data specific to CF it is recommended that calcium intake should follow age and gender specific RDIs [170]. It is important to note that the assumptions associated with these RDIs are that vitamin D status and calcium absorption are normal, which may not be the case in individuals with CF.

##### *Supplementation*

Calcium supplements should be considered, particularly when other medications (e.g. bisphosphonates and vitamin D) for low BMD are commenced [213] (evidence category D). If the RDI for calcium intake is unable to be met via the diet, calcium supplementation should be commenced. Recommendations for calcium intake in other population sub-groups suggest that intakes of up to 1500 mg per day be targeted in those with low BMD [213, 214] (evidence category D), although there is no CF-specific evidence as to the intake of calcium required to achieve balance.

#### **4.5 Other nutritional factors**

##### **4.5.1 Antioxidants**

Pulmonary exacerbations in the individual with CF generate a phenomenon termed oxidative stress [215, 216], which is characterised by the presence of free radicals and release of hydrogen peroxide and proteinases from immunocytes (evidence category C). Within the lungs, oxidants not only damage membrane lipids, proteins and DNA, but also mediate a variety of specific effects that could diminish lung function and/or lung repair mechanisms, including increased mucous production, impaired cilia function, stimulation of thromboxane (vasoconstrictor), injury of fibroblasts and reduced surfactant activity [217].

Adequate concentrations of antioxidants are necessary to minimise oxidative injury in the individual with CF. Vitamin E is considered to be the most important fat-soluble antioxidant. However, it is likely that all other components of the antioxidant screen also require supplementation, including glutathione (which is associated with both the CF transmembrane conductance regulator gene and nutritional status), carotenoids (such as  $\beta$ -carotene and lycopene), vitamin C and selenium (which is a constituent of glutathione peroxidase).

Consensus regarding supplementation of antioxidants in individuals with CF is yet to be established. It is likely that both elevated requirements associated with the disease and decreased absorption of these micronutrients in individuals with CF need to be met with supplementation.

Research is required to establish if supplementation of antioxidants in individuals with CF should achieve concentrations higher than in the normal population.

#### **4.5.2 Essential fatty acids**

The essential fatty acid (EFA) status of individuals with CF is variable, ranging from normal to highly disturbed compositions [218]. In general, individuals who are pancreatic sufficient have normal or less disturbed fatty acid compositions (in plasma phospholipids, cholesteryl esters, triglycerides, non-esterified fatty acids and erythrocyte lipids) than individuals who are pancreatic insufficient [218]. Biochemically, EFA deficiency is common in CF, however, unless routinely screened for, it is often not detected as it rarely presents with clinical signs and symptoms.

Polyunsaturated fatty acid depletion in individuals with CF may result from maldigestion and malabsorption of dietary lipids, being underweight and a negative energy balance. Recommendations regarding routine supplementation with high doses of docosahexaenoic acid are limited by the need for further evaluation. Adverse effects of excessive intakes of EFA and long chain polyunsaturated fatty acids have been observed, and include enhanced lipid peroxidation and unbalanced synthesis of specific eicosanoids. Further research is needed to assess the effects of manipulating dietary fat on lung disease in individuals with CF [219] (evidence category A).

The current recommendation concerning EFAs and long chain polyunsaturated fatty acids is as for the general population. Subnormal levels should be avoided by ensuring that energy intake is adequate, polyunsaturated fats are consumed (with balanced proportions of polyunsaturated fatty acids from both the n-6 and the n-3 series) and antioxidant intake is increased. Vegetable oils, such as flax, canola and soy, and cold-water marine fish, which are rich in linolenic acid, are useful additions to the diet.

#### **4.5.3 Probiotics**

The benefit of probiotics in the treatment of respiratory and gastrointestinal problems in individuals with CF is yet to be determined. Probiotics are live microorganisms that, when ingested, produce some therapeutic or preventive health benefit. Probiotic supplements contain bacteria that may assist in balancing the levels of beneficial and harmful bacteria in the gastrointestinal tract, hence restoring balance to the intestinal flora. The normal balance of these bacteria may be disturbed by illness, poor diet, stress, aging, infection and the use of medications, such as antibiotics. Antibiotics are known to eradicate both harmful and beneficial bacteria from the gastrointestinal tract, leaving it vulnerable to the invasion of potentially pathogenic bacteria.

Although probiotic supplementation has been observed to reduce the incidence of intestinal inflammation [220] (evidence category B) and severe respiratory infections in children with CF [221] (evidence category B), more research is required to determine its impact on the health of individuals with CF and to establish effective dosages. Despite evidence regarding the clinical effects of probiotic supplementation in individuals with CF being limited, some CF centres in Australia recommend their use. Probiotics are available in various forms, such as yoghurt, capsules, tablets, beverages and powders. Of interest, a probiotic drink has been found to be better than yoghurt in reducing the nasal carriage of pathogenic bacteria in individuals who do not have CF [222] (evidence category B).

Although there is no indication that probiotics have any adverse effect on children with CF, the use of infant formulas supplemented with probiotics is not recommended for infants less than five months of age, and particularly not in infants who are premature or immunocompromised [223] (evidence category A).

#### 4.5.4 Complementary therapies

Individuals with CF may seek alternative treatments, either to complement or to replace standard care. The types of complementary and alternative medical therapies sought and used by individuals with CF may include meditation, hypnosis, biofeedback, chiropractic, herbs, vitamins, minerals, diet and lifestyle modification.

Until information regarding safety and efficacy of complementary and alternative medical therapies in CF is available, the dietitian, pharmacist and medical team should evaluate the products and treatments used by individuals in their care [153] (evidence category C).

#### **Recommendations**

##### *Macronutrients*

- 1. Energy requirements in individuals with CF are likely to be between 120 to 150% greater than healthy individuals, however, this is only a guide and individual factors, such as clinical status, should be taken into consideration (B)**
- 2. Encourage an unrestricted diet, containing adequate fat to meet energy requirements. Target 100 g/day if over five years of age (C).**
- 3. Encourage adequate intakes of carbohydrate to assist with meeting energy intake targets, but consider modifying the type and distribution of carbohydrate in individuals with CFRD (see section 7) (D).**
- 4. Encourage a moderate fibre intake between 10-30 g/day (D).**

##### *Vitamins*

- 5. Serum levels of fat soluble vitamins A, D and E should be measured routinely, at a time of clinical stability, in all individuals with CF, particularly those with pancreatic insufficiency (C). The PIVKA II test for vitamin K measurement should be considered, but is not routinely available.**
- 6. All fat soluble vitamin levels should be interpreted based on current supplementation dose, compliance to supplementation and PERT, clinical status, other serum levels (such as zinc and retinol binding protein for vitamin A interpretation), season of measurement (vitamin D) and renal (vitamin D) or liver disease (vitamin A, D and K) (D).**
- 7. Supplementation is recommended if vitamin levels are low (outside local laboratory reference ranges for vitamins A and E, or less than 50 nmol/L for 25-hydroxyvitamin D) (D). See Table 5 for recommended starting doses of all vitamins**
- 8. Monitor vitamin levels and review the supplementation regimen 3-6 monthly until levels normalise, then revert to annual monitoring (D).**

##### *Minerals*

- 9. Fluid and sodium supplementation should be determined by monitoring individual signs and symptoms (D).**
- 10. Recommended daily doses of sodium are**
  - a. 500-1000 mg/day for infants**

- b. up to 4000 mg/day for children, and
- c. 6000 mg/day for adolescents and adults (D).

11. Supplement fluid and sodium intakes further when exercising and during hot and/or humid weather conditions (D).
12. Perform iron studies and a CRP annually at a time when clinically stable (D). Supplement where ferritin is < 20ng/ml, or < 200ng/ml with a raised CRP and raised soluble transferrin receptor level (D).
13. Calcium intake in individuals with CF should meet RDIs for the general population and be increased to 1500 mg/day for those with low bone mineral density (D).

*Other nutritional factors*

14. Further research is needed to form recommendations on antioxidants, essential fatty acids and probiotics (D).

## 5. Implementing nutritional management of CF

### 5.1 Introduction and rationale for nutritional management

Nutritional interventions are warranted in CF as improvements in nutritional status, through optimal dietary intake and PERT, could increase the number of individuals exposed to the survival advantage first demonstrated by Corey and colleagues [15]. The attainment of optimal nutritional status ensures that individuals with CF have some energy in reserve for occasions when the maintenance of positive or zero energy balance is challenged by pulmonary disease [124]. Thus, it is important for nutritional interventions to be initiated early, when individuals with CF have mild or moderate pulmonary involvement. Aggressive rehabilitation in those with  $FEV_1 < 40\%$  predicted is not always successful and may not be medically indicated in the terminally ill, unless the person is awaiting organ transplantation [224]. Effective nutritional management of CF would ensure that both deterioration in nutritional status and the cause of negative energy balance are identified early so that nutritional interventions are prompt and targeted appropriately.

Interventions that at least minimise or delay deteriorations in nutritional status may have positive effects on growth, physical activity, pulmonary function, quality of life and survival. The provision of information regarding how to achieve a high energy, high fat, high salt, nutrient dense diet will result in many individuals with CF attaining optimum nutritional status, however it is not a guarantee that all individuals with CF will meet their energy requirements at all times throughout their life.

Comprehensive assessments of body composition, dietary intake and biochemical markers should be routinely conducted in order to detect deteriorations early, before weight, height and pulmonary function are compromised (see sections 3 and 5.3).

The consensus document by Ramsey and colleagues [162] introduced the concept of anticipatory guidance by specialist CF dietitians, so as to optimise oral intakes and minimise deteriorations in health. Much of the advice should be given in anticipation of age-related nutrition needs. Following is a description of the three response categories for the provision of nutritional support that are detailed in the report [162].

1. Routine management of all patients: high energy, high fat, high salt nutritional education and dietary counselling; and PERT and vitamin-mineral supplementation for those with pancreatic insufficiency.  
Anticipatory guidance of patients at risk of developing energy imbalance, but who are maintaining adequate nutritional status: energy dense dietary education, close monitoring of dietary intake and behavioural management counselling.
2. Supportive intervention for patients with decreased weight velocity and/or slightly compromised nutritional status: anticipatory guidance plus oral supplements, such as fortified milk drinks and desserts and glucose polymers.
3. Rehabilitative care for patients whose nutritional status is compromised: overnight supplementation via an enteral tube.  
Resuscitative and palliative care for patients whose nutritional status is significantly compromised: 24 hour continuous enteral tube feeds and/or total parenteral nutrition, particularly in those awaiting organ transplantation.

## **5.2 Pancreatic enzyme replacement therapy (PERT)**

### **5.2.1 Introduction**

An evaluation of the uptake and impact of the Australian CF PERT Guidelines was undertaken in early 2001 [31] (evidence category C). All CF centres, including rural practitioners, were surveyed. Of the 28 surveys returned, 26 indicated they had received the PERT guideline publications, with 21 having referred to the clinical guidelines [30] and 10 to the implementation paper [29]. Only three responses indicated that they had changed their approach to PERT from another method. Fifteen responses indicated that the guidelines had helped them identify patients at risk of fibrosing colonopathy and 20 reported the guidelines had led to a reduction or rationalisation of the amount of PERT used by their patients. Responses highlighted that the medical practitioner (n=25) or dietitian (n=24) were responsible for adjusting PERT dose and for education of patients and carers on appropriate self-management. The majority of clinics reported that their patient PERT dosages were consistent with the guidelines and seven respondents indicated they had undertaken quality assurance activities related to the PERT guidelines. Overall, the survey highlighted that the PERT guidelines had had a major impact on clinical practice and led to rationalisation of PERT use in Australia [31].

### **5.2.2 Indications for PERT**

All individuals with CF require careful management and review of pancreatic function from diagnosis. An early decline in pancreatic function has been noted in those patients who have either a class I or class II mutation. Therefore, it is recommended that those with mutations in these categories receive early assessment of their pancreatic function and intestinal absorption, to improve efficacy of the introduction of PERT [225] (evidence category C).

The use of PERT for patients who are found to be pancreatic insufficient has been regarded as standard practice for many decades. Evaluation of pancreatic function is covered in section 5.2.4.1.

### **5.2.3 Prescription and dosing of PERT**

PERT is introduced once clinical evidence of pancreatic insufficiency is confirmed. Due to the progressive nature of CF, individuals who are pancreatic sufficient at diagnosis will require periodic assessment of pancreatic function. This can be informed by knowledge of their genotype and class of their **CFTR** mutation.

In Australia, the PERT Clinical Guidelines can be used to guide the management of pancreatic insufficiency in CF [30]. The guidelines recommend using a dietary fat-based dosage to link consumption of grams of fat to units of lipase in the capsules [29] or body weight [226, 227] (evidence category D) as a basis and then individualising the dose based on assessments of efficacy. It is recommended that when commencing PERT, to start with the minimum dose in the recommended range.

The Australian PERT Guidelines also address numerous factors related to distribution, administration, storage, adherence and follow-up [29, 30] (evidence category D). Redistribution of pancreatic enzyme capsules over the day, based on the fat content of the foods consumed has been shown to lead to a significant improvement in the coefficient of fat absorption and hence absorbed energy [19] (evidence category C). Fat-based dosing may assist individuals with CF in achieving the high energy, unrestricted fat diet recommended by helping to improve patient knowledge of food composition. Patient knowledge, particularly of fat has been shown to be poor [104, 105] (evidence category C). Commonly available resources detailing fat contents of foods and food products can be useful for building knowledge of food composition.

Minimum effective doses are recommended in order to decrease the risk of fibrosing colonopathy, which continues to be found in association with “enzyme overdosing” [228] (see section 6.4). An upper limit of 10 000 IU lipase/kg body weight/day has been recommended to reduce the risk of fibrosing colonopathy. An audit of use of PERT in patients attending CF centres in the UK (1999-2000) demonstrated that patients on preparations containing 10 000 or 25 000 IU lipase per capsule commonly exceeded recommendations [229] (evidence category C). Further, they reported that use of high-strength PERT increased the risk of “overdosing”, with two thirds of patients in this group exceeding recommendations compared to one third in the standard strength preparation group.

Generic enzymes are not bio-equivalent to propriety enzymes. Thus, it is recommended that only propriety enzymes be prescribed and that the prescription be marked ‘no substitution’ or with an equivalent statement.

Further advice to guide implementation of the guidelines has been published previously [29] and will help guide practice in this area.

See Appendix 3 for a list of pancreatic enzyme products available in Australia.

#### **5.2.4 Evaluating pancreatic function and monitoring efficacy of PERT**

##### *Pancreatic Function Tests*

Reviews of pancreatic function testing have highlighted the advantages and disadvantages of tests currently used [225, 230] (evidence category D). The recommendations made have been summarised, based on common clinical questions.

#### **What tests can be used to ascertain whether the patient is PI versus PS?**

##### *Direct test*

**The Pancreozymin–secretin** test provides the most accurate direct assessment of exocrine pancreatic function. However, it is complex, invasive, expensive, time consuming and only available in limited tertiary centres. This makes it impractical for routine clinical use in most centres.

##### *Indirect Tests*

**a. Faecal Elastase 1** can be measured using an **ELISA** kit, which utilises two monoclonal antibodies against human pancreatic elastase. Faecal Elastase 1 has advantages over faecal chymotrypsin. These include a significant correlation between duodenal and stool elastase, increased stability compared to chymotrypsin, low day to day variation in concentration meaning a single stool sample can be used and finally the Faecal Elastase 1 concentration is not influenced by PERT. The most frequently used cut-off value is 200 µg/g, compared to a usual concentration in healthy children of >500 µg/g. One study in newborn infants with CF reported that their Faecal Elastase 1 concentrations were closer to zero. The two main disadvantages were the high cost of the ELISA kit and that a false positive may occur with co-existing diarrhoea or when villous atrophy is present [225] (evidence category C).

**b. Faecal Chymotrypsin** has low sensitivity and specificity, high day-to-day variations and requires collection of multiple stool samples to address this. PERT contains chymotrypsin and, therefore, the test cannot be used in older children. A suggested cut-off stool concentration in newborn is <6.6 U/g.

**c. Faecal Immunoreactive Lipase** concentrations are age-dependent and also have a large range at a given age. Immunoreactive Lipase has a high sensitivity (87%) and specificity (97%) to detect pancreatic insufficiency. However, discrepancies exist across studies and are likely to be due to

variations in the method of detection and consequently associated normal ranges. Immunoreactive Lipase is not affected by PERT and the test can be used to identify pancreatic insufficiency versus pancreatic sufficiency.

**d. Stool Nitrogen** shows a good correlation between total stool fat and total stool nitrogen. This fact makes it an unnecessary test in CF.

### **What tests can be used for the quantification of Fat Excreted in order to assess efficacy of PERT?**

**a. The Titrimetric Method**, also the method of Van de Kamer, which saponifies wet faeces with an ethanolic alkali. The fatty acids are then liberated with HCL and extracted into petroleum ether, separated and fatty acids estimated by titration. There is daily variation, so a three-day (72-hr) stool collection is commonly used. While the actual analysis takes only about half an hour, the procedure is prone to collection and sampling errors and widely recognised as not being pleasant for everyone involved. The collection is made extremely difficult when diarrhoea or steatorrhea is present and the results can be affected by use of ointments. In healthy children the total fat excretion ranges from 0.14 to 1.3 g/day and varies with age, duodenal lipase & bile salt concentrations and dietary fat composition and total fat intake [231].

The Titrimetric Method can be used in conjunction with a three to five day dietary record and stool collection over the same period. This is used to assess total faecal fat output as a percentage of oral intake, with normal faecal fat excretion being <7% of the dietary fat intake of individuals who do not have CF [232]. Such faecal fat balance studies are useful for determining the need for PERT, to investigate signs of malabsorption when on PERT and to assess the response to alterations in PERT [77]. If an individual with CF is consuming medium-chain triglycerides, then it is important to inform the laboratory that stools should be analysed for fat using the Jeejeeboy method in order to avoid false negative results [233].

**b. The Fat Absorption Coefficient** depends on having a measure of the actual dietary fat intake, as this is expressed as a percentage of the fat excreted. A high fat intake should be consumed during collection (e.g. five g/kg in infants and 40-50 g/day in young children and over 70 g/day in older children). An advantage of the Fat Absorption Coefficient in the clinical setting is that it provides an opportunity to review the whole dietary intake and a precise measure is not required, rather an approximation. While the stool collection may be a problem, a marker can be used to link stool collection to intake, such as red or blue carmine, although this has been reported as problematic in some centres [234].

Normal values for infants and children have been reported [235].

<i>Age</i>	<i>Fat Absorption Coefficient (%)</i>
Premature	60-75
Infants to 6 months	80-85
6 months to 3 years	85-95
Over 3 years	>95

**c. The Steatocrit** uses the method of Phuapradit as described in 1981 [236]. However, it has a poor correlations with reference methods which has led to refinements in the method .

**d. The Acid Steatocrit** is a refinement of Phuapradit's method by acidification of the sample [225] (evidence category C). This method has a linear correlation with the % faecal fat estimate measured by the method of Van de Kamer. For healthy, infants over six months the normal values are <10% faecal fat estimate while in CF this may range from 20-30%. Although there is a daily variation, this still has a strong correlations with the three-day % faecal fat estimate ( $r=0.76$ ) [237] (evidence category B). However, further improvements can be made in the acid

steatocrit assessment if the mean over a number of different days is calculated. This test has two major advantages. Firstly, single stool samples can be collected and secondly, repeat measures can be used to monitor progress over time.

### *Monitoring efficacy of PERT*

To date, clinical signs and symptoms, such as growth, weight, bowel irregularities and fat-soluble vitamin status, have been heavily relied on to assess efficacy of PERT. The unpleasantness of collecting faeces reduces the number of individuals who are willing and able to undergo assessment of fat absorption as part of managing PERT. However, if individuals with CF and their families are educated periodically from diagnosis to adulthood about the importance of measuring fat absorption by stool analysis, then this could increase the degree of co-operation with these tests. The use of algorithms has been suggested to facilitate decision making in regard to both assessment of pancreatic function and the need to commence PERT [225] (evidence category C).

The effectiveness of PERT is thought to vary within and between individuals due to numerous factors related to the product (dose, potency, ratio of the various enzymes, microsphere size, shelf life, storage conditions) and to the individual (residual pancreatic function, the action of lingual and gastric lipases, gastric hyperacidity, low duodenal pH, bicarbonate production, abnormal intestinal solubilisation of long-chain fatty acids, reduced mucosal absorption, liver disease, short bowel syndrome, dietary intake, and adherence). The variation in the degree of steatorrhea caused by these factors may be primarily related to genotype, as a majority of  $\Delta F508$  homozygotes have more severe pancreatic insufficiency [162] (evidence category D). Individuals with CF who have a high level of persistent malabsorption may need adjuvant agents, such as H<sub>2</sub>-antagonists or proton-pump inhibitors, to improve the pH of the gastrointestinal environment and thereby increase the availability and effectiveness of pancreatic enzyme preparations.

The development of and refinements in PERT over the past two decades have enabled individuals with CF to tolerate much higher intakes of fat than when they were first available. Although, there is little evidence to indicate how to determine optimum PERT dosage.

Collaborative research between centres is needed to establish evidence-based PERT dosing practices and to ascertain if fat absorption can be improved to near normal levels (0 to 7% FFE) in the majority of individuals with CF. Murphy and Wootton [72] (evidence category D) support the pursuit of the most effective method of PERT dosing. They suggest that interventions directed at ameliorating abdominal discomfort, due to malabsorption, will help to enhance oral intakes. Future evaluations of all the PERT dosing methods need to include assessments of dose on a meal and snack basis, rather than just on daily intake, to assist in evaluating adherence [74, 76, 77] (evidence category C). It is appropriate to delay assessing absorption until high levels of adherence to PERT are achieved, such as no more than one meal or snack per day being under-dosed by 5000 IU of lipase or less [76] (evidence category C). Completion of a series of dietary records of intake could assist with self-monitoring of PERT. It can also be used by the dietitian to evaluate efficacy as part of clinical care and to assist in optimising both PERT and fat and energy intake [78] (evidence category C).

There is a gap in the evidence in assessing the ideal PERT dosing strategy to optimise absorption of polymeric enteral feeds, including both the timing of administration of pancreatic enzymes and the total dosage appropriate for the feeding regimen [29] (evidence category D).

### **5.3 Criteria for nutritional intervention**

Table 8 outlines the anthropometric criteria that indicate the level of nutritional intervention that may be required by an individual with CF. This table is intended as a guide only. All other factors

that affect, or are affected by, nutritional status, namely clinical status, co-morbidities, psychosocial factors and outcomes of previous nutritional interventions, need to be assessed in order to determine the most appropriate intervention (see section 3).

Individuals with conditions that increase the risk of nutritional failure need to be closely monitored so that appropriate aggressive interventions are instituted promptly. However, individuals with CF who are receiving palliative care for end-stage lung disease will require palliative nutrition support only.

Table 8: Anthropometric criteria indicating nutritional intervention that may be required <sup>1</sup>

<b>Category</b>	<b>Infants (&lt;2 years)</b>	<b>Children (2-18 years)</b>	<b>Adults</b>	<b>Interventions</b>
Acceptable/ normal nutritional status ≡ <b>Routine nutritional care</b>	Weight & length tracking along percentiles <b>and</b> within 2 centile bands of each other	BMI percentile 25-95 <sup>th</sup> %ile <sup>2</sup> <b>AND</b> Weight & height percentiles tracking along previous percentiles <sup>3</sup> <b>AND</b> No weight loss	BMI 20-27 <b>AND</b> Weight ≥45 kg even if normal BMI <sup>4</sup> <b>AND</b> No recent weight loss	Routine nutritional care & surveillance, +/- education and preventative counselling.
At risk <sup>5,6</sup> ≡ <b>Non-invasive nutritional interventions</b>	Weight and height percentiles decreasing with time <sup>3</sup> <b>OR</b> No weight gain <b>OR</b> <90% IBW	BMI percentile 10-25 <sup>th</sup> %ile <sup>2</sup> <b>OR</b> Weight loss over 1-3 months <b>OR</b> Plateau in weight gain over 2-4 months	BMI 18.5-20 <b>OR</b> Weight <45 kg regardless of BMI <sup>4</sup> <b>OR</b> ≥ 5% weight loss over 2 months	Consider nutritional & medical evaluation as some, but NOT ALL patients in this category are at risk for nutritional failure <sup>5</sup> . Non-invasive interventions: Goal setting re dietary intake, recommending/instituting prescriptive diet, oral supplements. Consider discussion of next line of treatment (i.e. aggressive nutritional support – gastrostomy tube insertion or nasogastric tube feeding) if nutritional status fails to improve or further deteriorates.
Nutritional failure /malnutrition <sup>5-7</sup> ≡ <b>Aggressive nutritional support</b>	Weight 2 or more centile bands below length <b>OR</b> <85% IBW <b>OR</b> Failure of non-invasive interventions to improve nutritional status	BMI percentile <10 <sup>th</sup> %ile <sup>2</sup> <b>OR</b> Weight falling 2 or more percentile positions <b>OR</b> Plateau in weight gain for 6 months <b>OR</b> Failure of non-invasive interventions to improve nutritional status	BMI <18.5 <b>OR</b> Weight <40 kg regardless of BMI <sup>4</sup> <b>OR</b> ≥ 5% weight loss over 2 months despite non-invasive nutritional interventions	Further nutritional & medical +/- psychological evaluation investigating factors contributing to malnutrition.  Treatment of nutritional failure: Aggressive nutritional support. Serious consideration needs to be given to the institution of enteral nutrition.
Overweight ≡ <b>Nutritional counselling</b>	N/A	BMI percentile >95 <sup>th</sup> %ile	BMI >27	Dietary and activity assessment, plus consideration of medical and psychosocial contributing factors. Consideration of counselling, nutritional management and exercise prescription if health status indicates it is appropriate to reduce weight to BMI ≤27 and/or to prevent further weight gain (adults); or achieve BMI ≤95 <sup>th</sup> %ile (children). Consider body image issues (especially females), body composition and excess fluid accumulation (e.g. liver disease). Not all patients in this category have excess fat stores or are at risk from complications of overweight <sup>8</sup> .

Footnotes for Table 8:

1. Adapted from international recommendations [8, 10, 11], recent evidence and Australasian requirements. Section 3 provides information regarding other parameters (e.g. Z-scores, body composition) that are also useful for assessing nutritional status and determining appropriate interventions for individual patients.
2. Clearly established cut-off values for BMI percentiles that relate to health status are not available [8], including the CDC website <http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/background.htm>, accessed 15/4/05. The values used in this table are consistent with the US CFF Consensus Report on nutrition in CF [8]. The cut-off point for nutritional failure at the 10<sup>th</sup> percentile for BMI is based on its association with pulmonary function [128]. The type of nutritional intervention to be implemented should be influenced by BMI percentile in conjunction with other indicators of nutritional status and the individual's clinical assessment factors. Research is required to assess the suitability of BMI percentiles in the nutritional assessment of children with CF.
3. Falling height centiles may indicate nutritional stunting, despite acceptable height for weight. Avoid misclassification of individuals who are genetically short by evaluating parental height percentiles.
4. Low weight is a risk factor for poor survival in individuals with CF (especially females).
5. Placement in "at risk" and "malnutrition" categories is based on the presence of one or more of the criteria being met. One or more criteria in this category over rides meeting criteria that would place the individual in a better nutritional status category.
6. Routine care, surveillance and preventive counselling should continue to be provided to individuals who are receiving non-invasive interventions and aggressive nutritional support.
7. Some individuals who progress to aggressive nutritional support may require concurrent non-invasive interventions (e.g. oral nutritional supplements, prescriptive diets).
8. There is insufficient evidence to attribute any CF specific increase in morbidity or health risk to being overweight, however it should be noted that some lung transplant units have criteria for eligibility of BMI  $\leq$  27.

## 5.4 Routine management of oral intake

### 5.4.1 Dietary guidelines

Table 9 highlights the differences between the dietary guidelines for the general Australian population of children and adolescents and those for individuals with CF.

Table 9: Australian dietary guidelines for children and adolescents, including those with CF

<b>For children &amp; adolescents in Australia</b>	<b>For children &amp; adolescents with CF</b>
Encourage and support breastfeeding.	Encourage and support breastfeeding.
Children and adolescents need sufficient nutritious foods to grow and develop normally. Growth should be checked regularly for young children. Physical activity is important for all children and adolescents.	Children and adolescents with CF need extra energy, appropriate food and physical activity to grow and develop normally. Growth and weight gain should be checked regularly.
Children and adolescents should be encouraged to: <ul style="list-style-type: none"> <li>• eat plenty of vegetables, legumes and fruit</li> <li>• eat plenty of cereals</li> <li>• include lean meat, fish, poultry and/or alternatives, and</li> <li>• include milks, yoghurts, cheese and/or alternatives; reduced fat milks are not suitable for children under 2 years because of their high energy needs, but encourage reduced fat varieties for older children and adolescents.</li> </ul>	Children and adolescents should be encouraged to: <ul style="list-style-type: none"> <li>• eat plenty of vegetables, legumes and fruit</li> <li>• eat plenty of cereals</li> <li>• include meat, fish, poultry and/or alternatives, and</li> <li>• include milks, yoghurts, cheese and/or alternatives; reduced fat milks are not recommended for individuals with CF because of their high energy needs.</li> </ul>
Chose water as a drink. Alcohol is not recommended for children.	Encourage milk as a drink. Aim for 3 cups/day. Alcohol is not recommended for children.
And care should be taken to: <ul style="list-style-type: none"> <li>• limit saturated fat and total fat intake; low fat diets are not suitable for infants</li> <li>• eat only a moderate amount of sugars and foods containing added sugars, and</li> <li>• choose low salt foods.</li> </ul>	Encourage the use of: <ul style="list-style-type: none"> <li>• added fats and nutritious foods containing fat to boost energy intake (monounsaturated fats and oils, such as canola and olive oil are healthy alternatives for the whole family)</li> <li>• sugar and foods high in sugar to boost energy intake, and</li> <li>• extra salt added to meals and choose salty snack foods.</li> </ul>

(NHMRC, 2003)

(Formulated by DAA CF Interest Group, 2004)

### 5.4.2 Infants

#### *Nutritional counselling*

Neonatal screening for CF, which is conducted throughout most of Australia and in NZ, results in the majority of infants with the disease being diagnosed by six to eight weeks of age. Early diagnosis ensures that optimal nutritional care can be provided prior to the onset of significant failure to thrive [46] (evidence category B). At diagnosis, comprehensive nutritional counselling is directed at the primary carers and extended family. Given that early learning sessions are often limited by the emotional distress that parents experience at diagnosis [238], regular consultations throughout the first year are necessary in order to ensure optimum nutritional status. Initially, nutrition reviews may be as frequent as weekly and then become monthly by the end of the first year.

### *Breastfeeding*

Breastfeeding is recommended for infants with CF as it offers numerous advantages, including naturally occurring enzymes, immunological properties, essential fatty acids, the presence of taurine to enhance fat absorption and the enhanced bioavailability of other nutrients [239]. Exclusive breastfeeding for at least six months has been associated with decreased use of intravenous antibiotics in the first two years of life [240] (evidence category C).

The support of partners, the extended family and health professionals towards breastfeeding is invaluable for the mother and infant. Community organisations, such as the Australian Breastfeeding Association ([www.breastfeeding.asn.au](http://www.breastfeeding.asn.au)) and the La Leche League in New Zealand ([www.lalecheleague.org.nz/](http://www.lalecheleague.org.nz/)) should be recommended in order to enhance the breastfeeding experience. Appropriate PERT is necessary to alleviate malabsorption in infants with pancreatic insufficiency and more frequent feeding is required to boost energy intake in those who are not thriving. Infants in most parts of Australia will require supplementation with sodium chloride, however, supplementation is not routine in New Zealand. The amount required is generally higher for infants who are breastfed compared to those who receive breast milk substitutes.

### *Breast milk substitutes*

A standard whey-based breast milk substitute is suitable for the majority of infants with CF who are not breastfed. A protein hydrolysate feed may be required by those with short-gut syndrome post ileal resection for meconium ileus and for those with severe malabsorption. A feed containing a proportion of fat as medium chain triglycerides should be considered for infants with cholestasis or uncontrolled steatorrhoea [239].

### *Energy supplementation*

The energy intake of infants who are failing to thrive can be boosted by encouraging the breast fed infant to feed more regularly and/or by increasing the energy density of their usual fluids and food. Breast milk substitutes can be fortified to 1 ¼ strength or adding fat and/or carbohydrate, in order to provide a further 25% of energy intake [8]. Growth rates improve to an adequate rate in most infants once PERT has commenced.

### *PERT*

PERT is required by all infants with pancreatic insufficiency irrespective of the type of infant milk used, including many pre-digested formulae. Enteric-coated enzyme granules, microspheres or mini-microspheres should be mixed with a little acidic fruit puree or gel (e.g. apple or pear) and administered via a teaspoon. Mixing of pancreatic enzymes and fruit should occur only just before they are administered at intervals throughout the feed. Dividing the enzyme dose between the beginning, middle and at the end of the feeding session may promote optimum mixing of enzymes and chyme and also allows for variations in appetite. The infant's gums should be cleared immediately after ingesting pancreatic enzymes to avoid trauma to the infant's mouth and the mother's nipples if breastfeeding.

### *Introduction of solids*

Solids should be introduced to the infant with CF at about six months of age as for healthy infants [126]. PERT should be reviewed and information provided about the fat content of food. A nutritious high fat, high salt diet is recommended throughout infancy and childhood, with care being taken to develop appropriate eating habits. Dietary intake needs to be carefully monitored to ensure that energy dense fluids do not reduce the quality of the infant's diet. After 12 months of

age, cows milk can be introduced as the main drink if food intake is varied and the infant is clinically well.

### 5.4.3 Children

#### *Food-related behaviour*

Current dietary recommendations for CF instruct parents to override their child's energy intake regulation mechanisms in order to successfully overfeed them. Food refusal and fussy eating are common behaviours seen in many toddlers and may make it difficult to achieve recommended energy intakes for individuals with CF [82] (evidence category B). Toddlers and children aged five to eight years with CF have been observed to have significantly longer meal and chewing times, and be less willing to try new foods than non-CF children [92, 113] (evidence category B). Telling children to 'drink more milk' or 'eat more food' or even to 'try harder' adds to existing family tension triggered by food and eating.

Desirable nutrition and PERT behaviours should be nurtured in children with CF from a very young age in order to reduce the incidence of problems. Carers need to be aware that an appropriate strategy for dealing with a child's refusal to eat is to ignore the behaviour and not offer anything more to eat or drink until the next scheduled meal or snack, when the same or an equally nourishing food should be presented. Although carers may be reluctant to deal with their child in this way because of the emphasis placed on adequate growth in CF, they need to be encouraged to avoid inappropriate short-term strategies, such as coaxing their child to eat or preparing a favourite food, in order to prevent long-term meal refusal. Family communication and functioning may be improved by teaching parents to use verbal praise and direct commands with children [241] (evidence category C).

#### *Dietary intake*

A varied food intake is the foundation of the diet for all individuals with CF (see table 9). Energy intake can be increased for the child with CF by boosting their usual diet with added fat, providing larger serve sizes, adding extra snacks and by selecting energy dense foods and beverages, so that the remainder of the family can consume a healthy diet as recommended for the general population. Full fat milk is recommended for all toddlers and children with CF. Consumption of whole milk has been shown to result in higher fat and energy intakes in CF, with whole milk identified as the single most useful food for achieving the higher energy intakes necessitated by the disease [242] (evidence category C).

The potential need for invasive nutritional support (i.e. oral nutritional supplements and enteral tube feeding) should be periodically approached with the family, when the child with CF is well, in order to facilitate acceptance of these measures before pulmonary function deteriorates markedly [243]. Carers of both pre-school-aged and primary school-aged children should be advised to optimise communication with their child about CF nutritional self-care, such as continual monitoring of malabsorption, so that immediate action can be implemented to overcome a problem [244] (evidence category D).

#### *School-based issues*

By four years of age, children should be encouraged to learn to swallow pancreatic enzyme capsules whole in order to normalise their care at school. The *Go and Grow with CF* program [34] provides a strategy for teaching children to swallow capsules. Teachers and staff at child care centres and schools should be provided with information regarding the safety of pancreatic enzymes if accidentally swallowed by another child and how CF dietary needs differ from those for the

general population (see Table 9). A supportive school environment may enhance adherence to CF treatments, such as administering pancreatic enzymes, when away from home.

#### **5.4.4 Adolescence**

Rejection of CF treatments, including PERT and vitamin, mineral and nutritional supplementation, and changes in lifestyle and food habits are common during adolescence. This is unfortunate because nutritional requirements are highest during adolescence as it is a period of peak growth and sexual development. Also, during this time, there is an increased incidence of pulmonary infections, CFRD and liver disease. Adequate energy and calcium are required by adolescents in order for their body to achieve its growth potential and optimise bone density. Poor nutritional status prior to and during adolescence has been observed to delay sexual development by two years [245] (evidence category C). Females, who generally have lower nutritional status and life expectancy than males, need to be monitored closely as they are at risk of body image concerns that may conflict with ideal health related nutritional goals.

The adolescent should be involved in the process of making decisions regarding their CF care in order to minimise the consequences of sub-optimal self-management. Raised energy requirements could be met by planning with the adolescent strategies for increasing the energy density of meals and snacks throughout the day. Periodic review of PERT is also necessary so that the adolescent is confident about administering pancreatic enzymes and calculating the correct dosage, particularly when snacking in the company of peers.

#### **5.4.5 Transition to adult care**

Transition to an adult health care system usually occurs during late adolescence or early adulthood. The main concerns about transition appear to be infection control, leaving behind previous caregivers, meeting a new team and quality of care [246] (evidence category C). Staged transition can facilitate the individual in gradually acquiring appropriate CF self-management skills. The timing of transition should be centred on the individual's developmental readiness [37], perspectives and health concerns [247] (evidence category C). Attention should also be given to the concerns and expectations of parents as well as adolescents and young adults with CF [246]. A multidisciplinary approach and excellent communication between both teams will help achieve a smooth transition to adult care for the individual with CF. A summary of nutritional history and management by the paediatric dietitian should be a component of the handover.

#### **5.4.6 Adults**

Early after transition to adult care is an opportune time to review each patient's understanding of the nutritional aspects of CF care. Further education, pitched at a more mature level may be required. In addition, a number of new issues may influence nutrition. These may include commitments to study and/or work, independent living (requiring meal preparation skills) and travel. For each individual, the social issues specific to them should be considered in their nutrition management

Table 10 highlights the differences between the dietary guidelines for the general Australian population of adults and those for individuals with CF.

Table 10: Australian dietary guidelines for adults, including those with CF

<b>For Adults in Australia</b>	<b>For Adults with CF in Australia</b>
<p>Enjoy a wide variety of nutritious foods</p> <ul style="list-style-type: none"> <li>• Eat plenty of vegetables, legumes and fruits</li> <li>• Eat plenty of cereals (including beads, rice, pasta and noodles), preferably wholegrain</li> <li>• Include lean meat, fish, poultry and/or alternatives</li> <li>• Include milk, yoghurt, cheese and/or alternatives. Reduced fat varieties should be chosen where possible.</li> <li>• Drink plenty of water</li> </ul> <p>And take care to:</p> <ul style="list-style-type: none"> <li>• Limit saturated fat and moderate total fat intake</li> <li>• Choose foods low in salt</li> <li>• Limit your alcohol intake if you choose to drink</li> <li>• Consume only moderate amounts of sugars and foods containing sugar</li> </ul>	<p>Eat a wide variety of high energy nutritious foods</p> <ul style="list-style-type: none"> <li>• Eat plenty of vegetables, legumes and fruits</li> <li>• Eat plenty of cereals (including beads, rice, pasta and noodles), preferably wholegrain</li> <li>• Include meat, fish, poultry and/or alternatives. High fat varieties are recommended.</li> <li>• Include full fat milk, yoghurt, cheese and/or alternatives. Reduced fat varieties are not recommended for adults with CF, because of their low energy value.</li> <li>• Encourage full fat milk as a drink. Aim for 3 cups per day.</li> </ul> <p>And take care to:</p> <ul style="list-style-type: none"> <li>• Include added fats and nutritious foods containing fat to boost energy intake. Monounsaturated fats and oils, such as canola and olive oil are healthy alternatives for the whole family.</li> <li>• Add extra salt to meals and choose salty snack foods</li> <li>• Limit your alcohol intake if you choose to drink</li> <li>• Include sugar and foods high in sugar to boost energy intake</li> </ul>
Prevent weight gain: be physically active and eat according to your energy needs.	Maintain an adequate weight. Prevent weight loss: be physically active and eat according to your energy needs.
Care for your foods, prepare and store it safely	Care for your foods, prepare and store it safely
Encourage and support breastfeeding	Encourage and support breastfeeding

(NHMRC, 2003)

(Formulated by DAA CF Interest Group, 2004)

### 5.4.7 Education

Ideally, CF nutritional care should involve a series of programs to address dietary- and PERT-related issues as they relate to the individual's stage of development. This concept is supported by McKelvey and Borgersen [248] who advocate approaching self-management training of families with a child who has a chronic illness according to the family life-cycle (infancy, toddlerhood, primary school-aged, adolescence and adulthood).

The optimum time for commencing nutrition education programs may be in the pre-school years [249] when families are faced with fewer competing demands. Carers of school-aged children have stated that lack of time is the main reason for refusing to participate in CF nutrition programs and interest in learning is often highest soon after diagnosis [34]. Conducting several interventions during the pre-school period may be highly beneficial in that the educational messages can be proactive and motivational, so that families are encouraged to periodically participate in programs throughout the child's life.

Programs conducted for carers of pre-school-aged children should address the management of child behaviours, in addition to providing nutrition and PERT information, in order to minimise the impact of inappropriate behavioural issues on the dietary intake of many children who have CF [106]. Parents of children with CF face the enormous task of managing behaviours related to the numerous treatments for the disease, in addition to normal child behaviours. Programs that address normal parenting strategies at each stage of the child's development may help ensure that parental reactions to issues, such as food refusal (which may be partly due to anorexia associated with the disease) do not compound the problems.

The benefits of effective pre-adolescent training may be realised when children become autonomous from their parents and have sufficient skills to maintain optimal management of their disease [250]. Clinic-wide programs could be supplemented by material directed at particular subgroups of the CF population, such as nutrition and body image for pubertal and post-pubertal females. Rigorous long-term studies are needed to prospectively assess the impact of preventative nutrition strategies on survival in well individuals with CF.

Although colouring books, stories, nutrition games, high energy tasting sessions and computer assisted learning packages are useful media to use with children, nutrition-related behavioural change is most likely to occur when behavioural psychology is integrated with nutrition education. A summary of four nutrition related behavioural programs can be found at <http://adt.curtin.edu.au/theses/available/adt-WCU20030717.135204/> [251]. These programs utilised social learning theory concepts to address the psychosocial factors that determine behaviour as it comprehensively addresses both the psychosocial factors that determine health behaviours and the strategies to use to promote behaviour change [252] (see Appendix 5). Also of interest is the systematic review of the behavioural techniques previously utilised in CF care that was recently undertaken [253] (evidence category A).

Implementation of nutrition-related behavioural programs, at several stages throughout a child's life, requires health-care providers to make major adjustments in their approach to caring for individuals with CF. Team support for a preventive approach to nutrition is needed as families are influenced by the attitude of other professionals towards extracurricular activities [34].

#### **5.4.8 Inpatient management**

During hospital admissions, alterations to usual nutritional management may be required to manage issues such as weight loss and anorexia associated with infective exacerbations of lung disease.

The hospital food service system should be able to accommodate the nutrition and food requirements of individuals with CF during inpatient stays (evidence category D). This includes the ability to provide a high energy diet as required, including availability of high energy snacks and oral nutritional supplements as appropriate, and to accommodate the CF-specific dietary needs of those with CFRD (see section 7).

### **5.5 Oral nutritional supplements**

#### **5.5.1 Background**

The results of a meta-analysis of treatment approaches to malnutrition in CF indicated that oral supplementation and behavioural interventions with children and adolescents requiring nutritional rehabilitation could be as effective as enteral and parenteral feeding in improving weight gain [100] (evidence category B). Oral nutritional supplements are usually high in energy and/or protein and come in the form of fortified milk-based drinks, puddings, bars and glucose polymers. They can be

either “ready to consume” products, those that are mixed with other foods or ingredients to make a high energy preparation, or home- or hospital-prepared recipes that are energy dense (e.g. fortified milkshakes, fortified infant formula, soups and puddings). Palatability, volume and nutritional composition need to be taken into account when choosing a product. Adherence to oral nutritional supplements by individuals with CF is likely to be influenced by the cost and accessibility of the product. Centres throughout Australia vary in their provision of products and, subsequently, the costs incurred by the patient. In New Zealand, all oral supplements are fully funded by Pharmac (excluding Scandishake® at this time).

The efficacy of oral nutritional supplements in children and adults with CF is not well established [254, 255]. The products are considered to be useful for when nutritional status and/or dietary intake continue to be sub-optimal, despite attempting to address all issues affecting oral intake, such as PERT, chest treatments and co-morbidities (evidence category D). Expert clinical judgement is often relied upon when initiating the use of oral nutritional supplements in CF [256] (evidence category D).

The efficacy of oral nutritional supplements in mildly malnourished children with CF has recently been examined in a multi-centre trial (the CALICO trial) [257]. Participants were randomly assigned to receive either oral nutritional supplements, in order to increase their energy intake by 20%, or standard dietary advice for a period of one year. There was no additional improvement in nutritional parameters in the supplemented group compared with the group who received standard dietetic advice alone, although reported energy intake was 18% greater in the supplemented group (evidence category B). It is important to note that the results of the study cannot be generalised to children with moderate or severe malnutrition, to adults (who were not studied) or to short-term oral nutrition interventions, such as during acute infective exacerbations.

### **5.5.2 Use**

The results of the CALICO trial indicate that oral nutritional supplements should not be regarded as a routine therapy for all CF patients [257]. The decision to use oral nutritional supplements in individual patients with CF relies on expert clinical judgement [256] (evidence category D). In those with chronic malnutrition, prescribed oral nutritional supplements should be consumed in addition to usual oral intake rather than as a substitute, so that an increase in total energy intake is achieved. Supplementary fluids or puddings are best consumed after a meal, as a between meal snack or before bed so that appetite for regular dietary intake is not diminished. Alternatively, individuals with CF who experience anorexia associated with acute illness may find that oral nutritional supplements are useful as snacks or as a meal replacement until their health and appetite are restored. In such cases, the objective of prescribing oral nutritional supplements is usually to avoid a decline in total energy intake associated with the illness-related anorexia.

### **5.5.3 Monitoring**

When established on oral nutritional supplementation, more frequent reviews of weight and dietary intake should be undertaken until optimal nutritional status is achieved. Infants should be reviewed two to four weekly and children four to six weekly while receiving oral nutritional supplements. Adults should be reviewed within a month of commencing oral nutritional supplements, and at least three-monthly once established (evidence category D). Monitoring of individuals receiving oral nutritional supplements should encompass a review of tolerance, adherence, progress towards objectives and ongoing need. In those whose nutritional status and/or dietary intake fail to improve or continue to decline, consideration should be given to instituting other nutrition support options, including enteral nutrition [11] (evidence category D).

## 5.6 Appetite stimulants

Individuals with CF can experience anorexia associated with the illness that may interfere with their efforts to achieve optimal nutritional status. This implies a possible role for appetite stimulants in the management of CF. The different types of products available are as follows:

1. *Megesterol Acetate* (Megace) is a progesterone derivative that has been used successfully to induce weight gain in patients with HIV and cancer. Megesterol acetate has been observed to increase appetite, body fat and weight in individuals with CF. Reported side effects included adrenal suppression, glucose intolerance and diabetes [258] (evidence category B).
2. *Cyproheptadine* (Periactin) is an antihistamine with a secondary effect of appetite stimulation. Cyproheptadine has been observed to be associated with a significant increase in weight and height in individuals with CF, with no adverse side effects apart from transient, mild sedation [259] (evidence category B).
3. *Growth hormone* stimulates growth and can be used as an anabolic agent. Growth hormone has been associated with increased weight, height and lean tissue mass in CF subjects who were reported to be adhering to dietary recommendations to optimise energy intake [260] (evidence category B).
4. *Methyl Prednisolone & Prednisolone* (Corticosteroids) are used to manage allergic type inflammation such as acute bronch-pulmonary aspergillus, uncontrolled asthma and CF arthropathy in non-transplanted individuals with CF. Corticosteroids have been reported to have appetite-enhancing properties in patients suffering from cancer cachexia, but associated weight gain has not been described in CF [261] (evidence category B). The use of corticosteroids with the primary aim of stimulating appetite is not recommended due to numerous debilitating side effects, namely redistribution of body fat to the face and upper neck, reduced bone mineral density, impaired glucose tolerance and salt and fluid retention [262] (evidence category D).

## 5.7 Enteral feeding

### 5.7.1 Benefits

If on-going comprehensive assessments indicate that nutritional status is deteriorating or failing to improve, after routine management and oral nutritional supplementation have been optimised, then enteral feeding is likely to be required. The positive nutritional outcomes observed in malnourished individuals with CF after an extended period of enteral feeding have included increases in lean body and muscle mass, body fat, growth velocity and total body nitrogen [20-25] (evidence category C). Improvement or stabilisation in lung function has also been observed with enteral feeding, possibly due to enhanced nutritional status reducing the number of pulmonary exacerbations, improving respiratory muscle strength and enhancing lung growth. Enteral feeding may be most successful in improving nutritional status and lung function when introduced early (before  $FEV_1 < 40-50\%$  predicted) [23, 263] (evidence category C), rather than as a last resort. Routine use of enteral feeding in the early stages of deteriorating nutritional status requires further evaluation.

Patient commitment to the long-term provision of enteral feeding is needed in order to achieve significant improvement in catch-up growth, lung function and body composition [11]. Individuals with CF and their families should be informed, about the benefits of attaining and maintaining optimum nutritional status by using enteral feeding, through nutrition education programs well in advance of such support being needed. Educational material needs to include information regarding the advantages and disadvantages of enteral feeding, the types of feeding tubes and formulas and how the feeding systems work [8]. The choice regarding enteral feeding should be based on factors specific to the individual with CF and a decision made together with the dietitian and physician.

Patient suitability for enteral feeding and ongoing adherence should be systematically assessed. Desired outcomes regarding enteral feeding should be identified with the individual who has CF prior to commencement.

### **5.7.2 Route**

The main routes of enteral feeding are via a naso-gastric tube or a gastrostomy tube. Rigorous evidence demonstrating the superiority of one type of enteral access over another is not available. Nasogastric feeding may be simpler than gastrostomy insertion and may be most successful when used for short-term support during respiratory exacerbations, when growth or BMI requires a boost or as a trial prior to gastrostomy feeding [11]. Individuals with CF who have nasal polyps may find a nasogastric tube difficult to insert and thus prefer gastrostomy feeding. Gastrostomy feeding is more suitable for long-term nutritional support, however tube placement may be unsuitable or high-risk for individuals with oesophageal or gastric varices [11].

### **5.7.3 Complications**

Problems encountered with enteral feeding include cessation soon after initiation due to poor appetite, GOR, vomiting, nasogastric tube dislodgement, particularly with coughing, gastrostomy tube blockage and site leakage, inconvenience with preparing and cleaning feeding sets and dissatisfaction with body image [101]. As untreated GOR is associated with poor clinical outcome after gastrostomy placement [263] (evidence category C), ambulatory pH measurements or contrast studies may be useful in identifying individuals with CF who are at risk. If GOR and/or early morning vomiting occur, a referral to a gastroenterologist should be made.

Individuals with CF receiving enteral feeding should be monitored for carbohydrate intolerance by assessing blood sugar levels when the full regimen is in place. If repeated blood sugar levels are elevated during the delivery of the formula, then it is likely that insulin needs to be administered prior to the commencement of feeding [11].

### **5.7.4 Amount**

Where weight gain is the goal of enteral feeding, options for determining the amount of energy to be delivered by enteral feeding include calculating:

- the difference between estimated energy requirements and oral intake
- the estimated kilojoules required each day to achieve a specified weight gain per week, or
- one-third to one-half of estimated energy requirements.

Nocturnal infusion of enteral formula is preferred in order to promote a normal eating pattern during the day. If bolus feeding is necessary, the formula can be provided after a meal or as a between meal snack.

### **5.7.5 Type**

The type of formula used should be based on clinical health, nutritional requirements, age and tolerance. Polymeric formulas are suitable for most individuals with CF when administered with PERT. Elemental and semi-elemental formulas often contain a higher proportion of fat as medium chain triglycerides (MCT), and require minimal pancreatic enzyme activity for effective digestion and absorption. For this reason they are often advocated for patients who exhibit malabsorption with enteral feeds, despite adequate PERT. Whilst there is little evidence as to the efficacy of elemental or semi-elemental feeds over polymeric feeds, Erskine and colleagues found no difference in fat malabsorption between a polymeric formula administered with PERT, and a semi-elemental formula delivered without PERT [264] (evidence category D). As PERT is usually not required with elemental or semi-elemental formulas (except in infants, see section 5.4.2). However,

these may be advantageous in situations where it is not possible to administer PERT, for example in a ventilated patient.

High fat formulas have been advocated for individuals with severe lung disease as less carbon dioxide is produced, lowering the respiratory quotient [265]. However, in a study examining the effects of low, medium and high carbohydrate formulas on respiratory function in CF there was no increase in hypoxia or CO<sub>2</sub> retention [266]. Until strong evidence regarding the effects of enteral feeding on respiratory function in CF is available, caution should be taken with the hypercapnic patient in order to avoid excessive energy intakes or high carbohydrate loads [265, 267].

Pre-prepared products are the most convenient, but are also more expensive. Delivery of food (e.g. a vitamised diet) via an enteral feeding tube is not recommended. As with oral proprietary supplements, adherence to enteral tube feeding is likely to be influenced by the cost and accessibility of formula and supplies to the individual with CF. Centres throughout Australia vary in their provision of products and the costs incurred by the patient. In New Zealand, all enteral formulas are fully funded by Pharmac and all provisions provided to the patient at no cost.

Specialised follow-up of the individual with CF, such as at a gastrostomy clinic, is advisable in order to ensure that stoma and tube related problems are correctly managed. The Nursing and Midwifery Practice Development Unit in the UK has developed best practice guidelines for nasogastric and gastrostomy feeding in children and can be referred to for further information regarding routine care of these devices [268]. The Australasian Society for Parenteral and Enteral Nutrition (AuSPEN) has developed clinical practice guidelines for home enteral nutrition and while not specific to CF are a useful resource to facilitate best practice in this area (<http://www.auspen.org.au/menu/best-practice-guidelines>). Many individual hospitals have resources and practice guidelines and protocols for enteral feeding, either for the general patient group, or specific for CF. Existing local hospital policies and guidelines regarding the care and use of gastrostomies and nasogastric tubes should be conformed with at all times.

#### **5.7.6 PERT**

The appropriate dosing regimen of pancreatic enzymes with enteral tube feeding has not been determined. Stapleton and co-authors outline two possible options for calculating doses for enteral tube feeding, which are detailed in the publication addressing the implementation of the Australian Clinical Practice Guidelines for PERT and reproduced in Appendix 4 [29]. Regimens tolerated and preferred by individuals who have CF vary considerably. Factors influencing PERT doses include formula type (polymeric, semi-elemental, elemental, proportion of medium-chain triglyceride oil), rate and duration of feeding, quality of sleep and frequency of administration. Research evaluating these and other possible pancreatic enzyme dosing options in CF is required.

Appropriate PERT for the individual with CF who is receiving enteral feeding but is dysphagic and/or ventilated has not been determined. Clinical experience indicates that it may be possible to enhance efficacy of PERT in such situations by administering a proton-pump antagonist or an H<sub>2</sub> blocker. Feeding continuously over 24 hours using a low fat polymeric formula (< or equal to four g fat/hour) or using an elemental or semi-elemental formula may optimise digestion and absorption in such circumstances without any PERT. Crushing enzyme microspheres, or tablets, and delivering them via a feeding tube is not recommended.

#### **5.8 Parenteral nutrition**

Individuals with CF who have a non-functioning gastrointestinal tract (e.g. due to prolonged bowel obstruction or gastrointestinal surgery) may require total parenteral nutrition if usual indications for this therapy are present [269]. Parenteral nutrition is usually reserved for those with a non-

functioning gut because it is costly and is associated with several risks, namely catheter sepsis and/or metabolic complications (e.g. hyperglycaemia) [269].

Parenteral nutrition may be considered in malnourished individuals with CF if other avenues of nutrition support are impractical or exhausted, despite a functioning gastrointestinal tract. For example, if the individual with CF is critically ill, is experiencing anorexia, but has no enteral access, or possibility to gain and maintain access. The evidence suggesting that supplementary parenteral nutrition is associated with improvement in weight and respiratory muscle strength [270-272] (evidence category C) and lung function [270] (evidence category C) is not strong. Thus, supplementary parenteral nutrition should be used only after careful consideration of the risks and the benefits. General guidelines for monitoring the effects of parenteral nutrition, particularly on blood sugar levels, would apply in the individual with CF.

## **Recommendations**

### ***Pancreatic enzyme replacement therapy***

- 1. Use indirect methods in the clinical setting to determine pancreatic status (D).**
- 2. Total fat excretion should be quantified in order to assess efficacy of PERT (C). While faecal fat estimate remains the gold standard for quantification of fat malabsorption, the mean daily acid steatocrit has been shown to correlate with faecal fat estimate and looks promising.**
- 3. Educate families from diagnosis through to adulthood, about the importance of periodic assessment of fat absorption by stool analysis. In individuals with pancreatic insufficiency, use the PERT in CF: Australian Guidelines (see Appendix 2) to prescribe PERT and monitor efficacy. Use a dietary fat based dosage for PERT to assist with patient education, self-monitoring and clinical review of intake and PERT usage (D).**
- 4. Educate families from diagnosis through to adulthood, about the importance of regular review of PERT usage in order to reduce the risk of fibrosing colonopathy secondary to excessive PERT (D).**

### ***Routine nutritional management***

- 1. Encourage breast milk from birth in infants with CF (C).**
- 2. If not breastfeeding, then a standard whey-based breast milk substitute is suitable for the majority of infants with CF (C).**
- 3. Optimise the rate of growth in infants by ensuring appropriate PERT, demand feeding and providing routine anticipatory dietetic counselling and education (D).**
- 4. Introduce solid food at about six months of age and full cream cow's milk as the main drink at about 12 months of age (D).**
- 5. Add fat to family meals and provide additional snacks and energy-dense beverages, such as milk, to children with CF in order to achieve a diet high in energy (D).**
- 6. Encourage children to swallow PERT capsules whole before commencing school (D).**
- 7. Utilise frequent, long-term behavioural strategies and interventions to prevent inappropriate food and mealtime behaviours in children (D).**
- 8. Integrate behavioural psychology with nutrition education to promote behaviour change (D).**

9. **Involve adolescents in the management and monitoring of CF care to promote adherence (D).**
10. **Enhance the transition process by ensuring that the individual is developmentally ready and that good communication with the entire health care team is established (D).**
11. **The hospital food service system should be able to accommodate the nutrition and food requirements of individuals with CF during inpatient stays (D).**

#### *Nutrition support*

1. **Oral nutritional supplements may be necessary when nutritional status and/or dietary intake continue to be sub-optimal, despite attempts to address all issues affecting oral intake (D). The nutritional status and dietary intake objectives of instituting oral nutritional supplements should be clearly identified prior to commencement. Affordability of commercial products should be considered prior to prescription.**
2. **Individuals receiving oral nutritional supplements should be closely monitored in order to optimise tolerance, adherence and progress towards nutritional and dietary objectives, and to review ongoing need (D).**
3. **The provision of supplementary nutrition via enteral feeding should be considered when other avenues of nutrition support (e.g. oral supplements) have failed, and the patient meets the criteria defined in Table 8 (section 5.3) (C).**
4. **Polymeric formulas should be suitable for most individuals with CF, although elemental or semi-elemental formulas may be useful in some circumstances. High fat formulas may be more appropriate than high carbohydrate formulas for individuals with severe lung disease who are hypercapnic (D).**
5. **PERT should be administered with enteral feeding, as outlined in the Australian Clinical Practice Guidelines for PERT (appendix 2) (D).**
6. **A gastrostomy is preferable to a nasogastric tube for the provision of supplementary enteral nutrition on a long-term basis (D). However, the individual with CF should be well enough to undergo general anaesthesia for gastrostomy placement in theatre (D).**
7. **Parenteral nutrition should be used only when the gastrointestinal tract is non-functional or all other avenues for nutrition support are impractical/exhausted (D). There should be careful consideration of the risks and benefits.**

## **6. Management of gastro-intestinal & hepato-biliary complications**

### **6.1 Meconium ileus**

Treatment for meconium ileus in the infant includes administration of enemas or, if necessary, surgical removal of the affected part of the intestine [273]. Resection, if extensive, may result in short-bowel syndrome which then needs management. Infants with short-bowel syndrome may initially require a pre-digested feed, such as a protein hydrolysate formula containing medium-chain triglycerides [10] (evidence category D). After a short post-surgery period, many infants are able to tolerate standard infant formula or breast milk with appropriate PERT.

### **6.2 Distal ileal obstruction syndrome**

Distal intestinal obstruction syndrome (DIOS), previously known as meconium ileus equivalent, is characterised by intermittent abdominal pain and constipation as faecal material and mucus gather in the distal ileum and proximal part of the large intestine. It is likely that DIOS occurs as a consequence of decreased motility and ion secretion causing abnormal intestinal mucus in the gut of individuals with CF [274]. Other factors that may predispose individuals with CF to DIOS include inappropriate PERT [275] (evidence category C) and dehydration [276] (evidence category C). It may be possible to avoid intestinal surgery in individuals experiencing DIOS by administering a hyper osmolar solution and increasing fluid intake [11] (evidence category D). Significant recurrent abdominal symptoms require full investigation by a gastroenterologist.

### **6.3 Constipation**

Persistent abdominal signs and symptoms of malabsorption, such as pain and loose faeces, may be due to constipation. Prevention and early treatment of constipation is required to avoid the more serious complication of DIOS. Individuals with a history of previous major abdominal surgery, meconium ileus in infancy or DIOS require close monitoring. Treatment of constipation in individuals with CF may include nutritional counselling to increase dietary fibre (see section 4.2.5) and sodium and fluid intakes (see section 4.4.1). Regular use of stool softeners may need to be considered in some cases [273, 277] (evidence category D).

### **6.4 Fibrosing colonopathy**

Fibrosing colonopathy is characterised by severe sub-mucosal thickening of the bowel wall by mature fibrous tissue [278]. Retrospective studies suggested that fibrosing colonopathy is associated with excessive doses of high strength pancreatic enzyme preparations and the type of enteric coating used on the microspheres [226, 227]. Doses exceeding 10 000 IU lipase/kg IBW/day without specialised advice and further investigation should be avoided [10, 11] (evidence category D).

The rapid emergence of this condition in the 1990s had an important influence on the management of PERT in CF. Adherence to PERT recommendations and the restriction of high strength preparations (>25 000 IU lipase/capsule) in adult populations have contributed to the reduced incidence of fibrosing colonopathy [10] (evidence category D).

## 6.5 Gastro-oesophageal reflux

### *Background*

GOR is defined as an abnormal increased frequency or duration of regurgitation of gastric contents into the oesophagus [279]. Acidic gastric contents in the oesophagus may result in inappropriate transient relaxation of the upper oesophageal sphincter, which may result in aspiration into the lungs [279]. Complications of GOR include oesophagitis and Barrett's oesophagus and oesophageal strictures [280].

### *Prevalence*

Prevalence rates for GOR in individuals with CF range from 35 to 81% [281-286] (evidence category C). Possible reasons for the high prevalence of GOR in CF include inappropriate relaxation of the gastro-oesophageal sphincter, delayed gastric emptying and bronchodilator therapy [279, 287, 288] (evidence category D). Coughing and increased thoracoabdominal pressure could also add to the degree of GOR in individuals with CF [286] (evidence category C).

### *Symptoms*

GOR may be either symptomatic or silent [282] (evidence category C). Typical symptoms of GOR include heartburn, dyspepsia, acid taste in the mouth and cough; but can extend to dysphagia, anorexia, nausea and vomiting. The symptoms of GOR have the potential to limit dietary intake, and thereby contribute to nutritional failure as well as to pulmonary complications of CF [289]. GOR symptoms may impair the ability to tolerate sufficient food and/or oral or enteral supplements in order to achieve nutritional targets. In children, treatment aimed at improving GOR has been associated with a significant increase in weight [284] (evidence category C). There is a lack of evidence regarding the association of GOR in adults with CF and nutritional status or supplementation; or whether GOR treatments affect nutritional intake or status.

### *Management*

Management of GOR involves assessing the individual's clinical history, monitoring 24 hour oesophageal pH and oesophageal manometry. Endoscopy is required for confirmation of suspected reflux oesophagitis. There is a lack of evidence from studies specific to CF to demonstrate the efficacy of the various management strategies. Medical management options include acid suppression using proton pump inhibitors and/or H<sub>2</sub> receptor antagonists [37] and prokinetic agents, which are particularly used in infants [37, 280, 290]. Lifestyle modifications may include modification of physiotherapy techniques [291] (evidence category C); sleeping on the left side [292] and elevation of the bed-head during sleep, although evidence to support this measure is limited [292] (evidence category D). Surgical options for severe reflux not controlled by other means include the Nissen Fundoplication procedure [280].

The role of dietary factors in GOR in the general population remains controversial [290]. Food intake and diet may play a role, as timing of the occurrence of symptoms and reflux episodes on oesophageal pH monitoring often coincides with meals [293] (evidence category D). Specific dietary factors that influence the occurrence, severity and management of GOR in individuals have not been identified. Advice should be individualised, as it is important that adequacy of the diet is not compromised by unnecessary or extensive restrictions. It may be beneficial to avoid particular food and/or beverages that appear to provoke reflux symptoms in an individual [293] (evidence category D). Strategies that have been suggested include avoidance of alcoholic beverages, caffeinated and carbonated beverages and spicy foods [292] (evidence category D). Timing of meals and snacks may need to be modified to avoid reflux episodes during physiotherapy/airway

clearance and sleep, but intake and nutritional status should be monitored to ensure they are not compromised.

### *Enteral feeding*

Supine positioning may exacerbate GOR, consequently overnight enteral feeding may result in formula being regurgitated and aspirated into the lungs. In studies not specific to CF, the relationship between enteral feeding into the stomach and GOR is not clear [294] (evidence category D). In non-CF subjects, enteral feeding beyond the pylorus has been associated with a significant reduction in GOR and a trend toward less pulmonary micro-aspiration, when compared with feeding into the stomach [295] (evidence category B). Feeding beyond the Ligament of Treitz, to minimise reflux into the stomach, might also positively influence rates of aspiration pneumonia. Feeding directly into the jejunum may be considered if GOR is demonstrated in individuals receiving enteral nutrition delivered into the stomach. Delivering enteral formulas at a slowed rate over a longer duration may also reduce GOR. Research is required to investigate the impact of enteral nutrition on GOR in individuals with CF.

## **6.6 Liver disease**

Liver disease is a frequent and early complication of CF. Individuals with CF who experience overt clinical liver disease can have serious nutritional problems both generally and also relating to specific macronutrients, fat-soluble vitamins and clotting factors [296] (evidence category C). Liver disease may exacerbate the severity of malabsorption through inadequate bile acid secretion [297] (evidence category C). Early detection of liver disease, biochemically or by ultrasound, may prevent deterioration in nutritional status [298] (evidence category C).

Ursodeoxycholic acid is used to treat biochemical liver disease, but it is unclear if this treatment leads to an improvement in nutritional status [299, 300] (evidence category B). Liver transplantation in individuals with CF is associated with long-term beneficial effects on nutritional status [301] (evidence category B).

## **6.7 Pancreatitis**

Pancreatitis may be experienced by two-thirds of the 15% of individuals with CF who are pancreatic sufficient [302] (evidence category C). The diagnosis of CF in adults may be preceded by recurrent pancreatitis [303] (evidence category C). Pancreatitis is characterised by severe abdominal pain radiating to the back, vomiting and raised serum amylase [304] .

The treatment of a single episode of acute pancreatitis in individuals with CF is similar to that of other aetiologies. Jejunal or parenteral nutrition is commenced to minimise pancreatic secretion and promote pancreatic rest. Recurrent pancreatitis may require the commencement of low dose PERT [305] (evidence category C), but this is not always successful in preventing further attacks. The protease contained in pancreatic enzyme supplements may inhibit pancreatic exocrine secretions and, thus, decrease pancreatic autodigestion and pain [306] (evidence category B). Once the pancreas has become totally fibrotic, and/or exocrine secretory function has diminished, pancreatitis is very unlikely.

## **Recommendations**

- 1. Ensure that PERT doses are adequate and adhered to and that capsules are taken appropriately (D).**
- 2. Avoid rapid and excessive increases in PERT dose (D).**
- 3. Encourage fibre intake if stool volume is low (C).**
- 4. Optimise hydration status (both fluids and sodium) (D).**
- 5. Enhance awareness regarding the signs and symptoms of malabsorption and bowel impaction (D).**
- 6. Aim for the lowest effective dose of PERT and aim to avoid PERT doses in excess of 4 000 IU lipase/gram dietary fat and/or 10 000 IU lipase/kg IBW/day (D).**
- 7. Individualise dietary advice in individuals with CF who have GOR. Consider avoidance of specific foods and fluids and the timing of meals (D).**
- 8. Achieve and maintain optimum nutritional status in the presence of liver disease. Increase the frequency of monitoring fat malabsorption and fat-soluble vitamin status in individuals with CF liver disease (D).**
- 9. In the presence of significant gastrointestinal and hepatobiliary complications, ensure patients are referred for appropriate medical follow-up (D).**

## 7. Cystic fibrosis-related diabetes

### 7.1 Prevalence & impact of cystic fibrosis-related diabetes

Pancreatic impairment is often progressive and older individuals are at increased risk of developing CFRD, with the median age of onset being between 18 and 21 years [307] (evidence category C), [308] (evidence category C), [309] (evidence category B). The prevalence of CFRD in an Australian CF adult population has been observed to be 24% (15% CFRD with fasting hyperglycaemia, six percent CFRD without fasting hyperglycaemia and three percent IGT) [310](evidence category C).

CFRD is considered a distinct clinical entity (distinct from other forms of diabetes) because, although the primary cause is insulin deficiency, it is influenced by conditions unique to CF, and can occur intermittently. In individuals with CF, under-nutrition, chronic intercurrent infections and liver dysfunction can affect glucose tolerance; acute illness, treatment with high dose glucocorticoid therapy and pregnancy can cause insulin resistance. Those with CFRD rarely present in ketoacidosis, presumably due to retained basal insulin secretion and, possibly, impaired glucagon release [311]. If untreated, or inadequately controlled, diabetes can contribute to energy deficits through glycosuria and to protein catabolism through insulinopaenia [311-312] (evidence category B).

### 7.2 Diagnosis & screening

#### Diagnosis

The following glucose tolerance categories are recognised in CF [157, 158, 307].

<b>Category</b>	<b>Fasting Blood Glucose</b> <i>mmol/l</i>	<b>OGTT</b> Blood glucose at 2 hours <i>mmol/l</i>
Normal Glucose Tolerance	<7.0	<7.8
Impaired GlucoseTolerance	<7.0	7.8 - 11.1
CFRD without Fasting hyperglycaemia*	<7.0	>11.1
CFRD with Fasting hyperglycaemia*	>7.0	OGTT not required

\*can be intermittent or chronic diabetes

The UK guidelines also recognise a category of reactive hypoglycaemia, which results from dysfunctional endogenous insulin secretion [157].

#### Screening

Screening for CFRD may reduce overall morbidity and mortality rates by enabling early CFRD management, as weight loss and declining pulmonary function have been observed two to four years before actual CFRD diagnoses [309, 313, 314] (evidence category B).

International consensus regarding the screening and management of CFRD is yet to be attained, as illustrated by documents detailing the different approaches between UK, USA and Denmark [157, 158, 307].

UK guidelines also recognise that in addition to diagnosis using an OGTT, elevated fasting or random plasma glucose levels with abnormal serial glucose monitoring, symptoms of hyperglycaemia or elevated glycosylated haemoglobin, or HbA1c, would also indicate CFRD. It

should be remembered that impaired glucose tolerance/CFRD can be transient and may resolve, albeit temporarily. Close monitoring of individuals with CF with such features is necessary [157] (evidence category D).

The USA consensus recommends screening all individuals with pancreatic insufficiency who are >14 years using annual random blood glucose tests, when clinically stable and during admission for acute exacerbation [158] (evidence category D). When random blood glucose levels are elevated greater than seven mmol/L, serial measures of fasting and two hour post prandial blood glucose measures should be performed. The USA consensus states that OGTT screening of the entire CF population is not practical or justified at present, but should be considered in high risk circumstances to rule out CFRD when fasting hyperglycaemia is not observed [158].

The cost and inconvenience of the OGTT procedure, and the observation of significant variability in OGTTs within individuals with CF, are factors that need to be taken into consideration when clinic-wide OGTT is standard practice. Laang et al [315] (evidence category C) observed 60% of subjects had normal glucose tolerance on subsequent annual testing. Further research regarding CF specific glycaemia measures is required as conventional measures, such as OGTT, are thought to underestimate glycaemia in non-diabetic individuals with CF [159] (evidence category B). It should be noted that HbA1c testing is inappropriate for diagnosing CFRD, possibly due to the reduced life span of red blood cells in individuals with CF [316] (evidence category B).

A profile of blood glucose monitoring, before and 1.5 to two hours after meals and during overnight tube feeding will need to be undertaken to define the extent of hyperglycaemia, before therapy can be instituted [307] (evidence category C).

Until international consensus regarding CFRD screening is determined it is recommended that screening be conducted during a time of clinical stability. This should be done **either by OGTT or by serial glucose measurements (fasting and two hour post prandial blood glucose levels)** in the following circumstances in individuals over the age of 10 years, if not conducted annually:

- in children with CF who are experiencing poor growth and in adults with CF who have difficulty maintaining their weight [158] (evidence category D), and
- in individuals with unexplained deterioration in respiratory function [157] (evidence category D).

In addition, serial blood glucose levels (fasting and two hour post prandial values) should be monitored in the following situations:

- during infections
- steroid treatment
- before, during and after enteral feeding and
- in pregnancy.

As individuals with CF are at risk of intermittent CFRD at these times [10, 158, 307] (evidence category D).

There is a psychological impact on the individual with CF that should be recognised when diagnosis of CFRD is made (evidence category D).

See also Table 4 (section 3.4) for a summary regarding biochemical monitoring.

### ***7.3 Medical management***

When CFRD is diagnosed, the multi-disciplinary approach to managing CF needs to include the diabetes team. The principal goals of managing glycaemia in CF are symptom control, optimisation of nutritional status and avoidance of hypo- and hyperglycaemia. Insulin is the treatment of choice

for CFRD as the primary problem is insulin deficiency. The management of CFRD with insulin has been observed to reverse a decline in BMI and lung function in individuals with CF [317] (evidence category B). There is a lack of evidence regarding the use of oral hypoglycaemic agents in CFRD, but it is possible that sub-categories of CFRD (e.g. IGT and CFRD without fasting hyperglycaemia) respond to beta cell secretagogues [316] (evidence category D).

Until there is evidence indicating the impact of specific insulin regimens on either clinical status or HbA1c in individuals with CF, the treatment regimen should be individualised and determined by the degree of glucose tolerance, eating habits and lifestyle [157, 158] [96, 318, 319] (evidence category D). Those who have a regular eating pattern may find that twice-daily insulin is sufficient to achieve adequate glycaemic control. In contrast, individuals with CF who have erratic dietary habits, with large snacks in addition to meals, may benefit from a regimen of soluble insulin or analogue insulin given with meals, snacks or oral supplements.

HbA1c is considered to be the measure that best reflects overall glycaemic levels over the preceding two to three months [320] (evidence category D). Mackie and colleagues suggest aiming for a HbA1c level of 6.5 to 7.0%, but to take into consideration the many factors that may affect optimum control in individuals with CF [320] (evidence category D). It is possible that lower targets are required to achieve adequate control, as HbA1c has been observed to underestimate glycaemic control in individuals with CF [159] (evidence category B). In other forms of diabetes, HbA1c is the only marker of glycaemic control that has been shown to be associated with long-term complications of diabetes [321]. There are no evidence-based recommendations specific to CF as to the optimal frequency of measurement of HbA1c. For type 1 diabetes, six-monthly measurement of HbA1c has been suggested for patients with satisfactory control and meeting management objectives, with a greater frequency of measurement (three-monthly) being recommended for those with sub-optimal control or in whom treatment has recently been changed [321]. In the absence of recommendations or evidence specific to CF, a similar frequency of monitoring is likely to be appropriate for individuals with CFRD (evidence category D).

Table 11: Illustrative example of treatment targets for individuals with CFRD [157]

	<b>Optimal control</b>	<b>Modified control- people at high risk of hypoglycaemia</b>	<b>Symptomatic Control -when palliative care is appropriate</b>
Fasting glucose	4–6 mmol/l	4–7 mmol/l	<10 mmol/l if pulmonary function tests stable and weight loss not a problem
2 hour post meal glucose	4–7 mmol/l	7–10 mmol/l	<10 mmol/l if pulmonary function tests stable and weight loss not a problem
Hypoglycaemia	Mild daytime hypos only	Aim for none	Aim for none
HbA1c (DCCT* aligned)	<7.0%	<8.0%	Irrelevant

\* Diabetes Control and Complications Trial [322]

### *Complications of CFRD*

Over the past decade, large scale, long-term randomised control studies comparing treatments for patients with Type 1 and Type 2 diabetes in the general population have been published [322, 323] (evidence category A). In both Type 1 and Type 2 diabetes the onset and progression of

complications correlate strongly with duration and control of the diabetes and the coexistence of other risk factors such as hypertension and hypercholesterolaemia. Individuals with CFRD are thought to be at risk of all the microvascular complications of diabetes.

Although, there is a lack of evidence regarding the affect of improvements in the control of CFRD, it is likely that the onset and complications will be reduced. Reported complications of diabetes are likely to become more common as the survival of individuals with CFRD increases.

Retinopathy, nephropathy and neuropathy can develop in individuals with CFRD [308, 324] (evidence category B). The natural course of these complications are not as clearly established in CFRD, as in Type 1 and Type 2 diabetes, but available data suggest they are rare within in the first five years of the onset of the CFRD. Screening for retinopathy and nephropathy annually in diabetic patients has been recommended [157, 158]. Macrovascular complications are rare but may become more common as individuals with CFRD progress into the fifth and sixth decades of life.

Hypoglycaemia may occur as a side effect of insulin treatment. The occurrence of severe hypoglycaemia or loss of awareness of hypoglycaemia is a major, potentially life-threatening complication of diabetes [157] (evidence category D).

See also Table 4 in section 3.4.1.

#### ***7.4 Nutritional management***

Differences between the nutritional requirements for CF and those for diabetes mellitus should always favour CF dietary needs [157] (evidence category D). The UK CF Trust CFRD Consensus document [157] (evidence category D) details differences in the dietary management of non-CF related diabetes mellitus and CFRD. Where it is necessary to include sweet foods and beverages, in order to meet energy requirements, it is advisable to consume these as part of a meal or substantial snack as they can cause a rapid rise in blood glucose if taken on their own [157] (evidence category D). Carbohydrate foods with a low glycaemic index should be encouraged where possible and be distributed evenly and consistently throughout the day to help optimise blood sugar control. However, a flexible dietary intake can be managed by altering the insulin dose using individually determined insulin to carbohydrate ratio [158] (evidence category D). Further studies evaluating dietary education programmes in the treatment of CFRD are needed.

Upon diagnosis, all aspects of routine management of nutrition and PERT should be assessed (see section 5.2), together with lifestyle, exercise and eating times. Additional counselling and education is necessary regarding the following:

- integration of insulin regimens into the individual's usual eating pattern (taking into consideration the amount and distribution of carbohydrate) and physical activity habits
- promotion of a flexible approach to insulin adjustment to account for health status, appetite and physical activity
- attainment and maintenance of the best possible glycaemic control
- education regarding self-management for monitoring blood glucose levels, altering insulin doses and prevention of acute and chronic complications of CFRD (hypo- and hyperglycaemia and microvascular abnormalities) [308, 325, 326] (evidence category C), and
- the need for annual screening for microvascular complications [157, 158, 308] (evidence category D).

## **7.5 Enteral feeding**

If an individual with CFRD requires enteral feeding, then extra insulin may be required during feeding sessions to cover the carbohydrate load. Additional blood glucose monitoring before, during and after enteral nutrition will assist in determining the effects of nocturnal glycaemia and how best to adjust the insulin regimen [157] (evidence category D).

### **Recommendations**

#### **1. Screen for CFRD at a time of clinical stability by either:**

- **OGTT**
- **or serial glucose measurements (fasting and two hour post prandial blood glucose levels).**

**Screen annually in individuals > 10 years, or in the following circumstances:**

- **in children with CF who are experiencing poor growth and in adults with CF who have difficulty maintaining their weight, and**
- **in individuals with unexplained deterioration in respiratory function.**

**(D)**

- **2. Serial blood glucose levels (fasting and two hour post prandial values) should be monitored in the following situations:**during infections

- **steroid treatment**
- **before, during and after enteral feeding and**
- **in pregnancy.**

**(D)**

#### **3. Treat both long-term and intermittent CFRD with insulin (D).**

#### **4. Ensure on-going nutritional assessment and counselling is provided by a dietitian experienced in CFRD (D). The key components of nutritional management include adequate energy intake and adequate carbohydrate intake evenly distributed over the course of the day and inclusion of low glycaemic index carbohydrate sources where tolerated. Dietary fat and simple carbohydrate should only be restricted in CFRD if energy intake and nutritional status are not compromised (D).**

## 8. Osteoporosis

### 8.1 Prevalence & aetiology

Over the past decade, the significance of low BMD amongst adolescents and adults with CF has become evident [40-42, 45, 327, 328] (evidence category C). Prevalence rates vary according to the population studied and the definition used to indicate reduced BMD, namely:

- BMD Z-score of  $<-2$  at one or more sites, or
- BMD T-score (suitable for adults only) of  $-2.5$  at one or more sites [329].

The prevalence of reduced BMD in individuals with CF in Australia is reported to be 27% of adolescents and between 12 and 17% of adults using lowest T or Z score to classify BMD status [42, 45] (evidence category C). The reader is referred to a consensus statement on bone health and disease in CF for a comprehensive review of the current status of bone health management in individuals with CF [192].

Reduced BMD may be associated with osteoporotic or minimal impact fractures [330, 331], particularly vertebral and rib fractures [41, 328, 332, 333] (evidence category C). Fractures can impair sputum clearance, pulmonary function and quality of life in individuals with CF [41, 45, 192, 330]. The problems associated with osteoporosis become increasingly evident post lung transplantation when BMD may be reduced further by long-term corticosteroid treatment [332] (evidence category C) and possibly other immunosuppressive agents.

The aetiology of bone disease in CF has been associated with numerous factors, including malnutrition, vitamin D deficiency, sex hormone deficiency and delayed puberty, lung disease and infection, prolonged corticosteroid exposure, reduced physical activity and the delta F508 genotype for CF [40-42, 44, 187, 328, 331, 333-335] (evidence category C). Both reduced bone accretion and accelerated bone loss are thought to contribute to reduced BMD in individuals with CF [336] (evidence category C). In contrast to the general population, greater bone mineral deficits have been observed in males compared to females [40, 42, 333, 337] (evidence category C). The survivor bias against females [42] and differences in the hormonal environment [337] have been suggested as possible explanations for these observations.

### 8.2 Assessment of bone mineral density

DXA scanning is used to assess BMD of the lumbar spine and femoral neck with or without the forearm [192]. Monitoring and management decisions are usually based on the site with the lowest BMD level. DXA scanning of children less than eight years of age is not warranted for several reasons, including the low prevalence of subnormal BMD prior to adolescence [192], the lack of normative data of children to assist with interpretation of the results and the difficulty some children may have in lying still for the duration of the scan (which is about 12 minutes) (evidence category D). Typically, T-scores (comparison with young adult population data) are used for interpretation of results in adults, although Z-scores (comparison with age-matched population data) may be used as well. Z-scores are only appropriate for use with children as they have not yet reached peak BMD. Areal BMD can be artefactually low when vertebrae are small, as true volumetric density is not being measured. This should be taken into account when interpreting BMD results in patients with small bones.

The frequency of follow-up scanning is dependent on previous BMD results, the type of treatment that was instituted for reduced BMD and the emergence of further risk factors, which include corticosteroid treatment, a significant decline in lung function, poor nutritional status, delayed

puberty, diabetes, fragility fractures and lung transplantation. When clinical status is stable, follow-up scanning should be conducted at least:

- every three to five years if BMD was normal; Z or T scores  $> -1$
- every two years if BMD was moderately reduced; Z-score between  $-1$  and  $-2$ ; or T-score between  $-1$  and  $-2.5$ , and
- annually if BMD was severely reduced; Z-score  $< -2$  or T-score  $< -2.5$ .

More frequent scanning is recommended if significant new risk factors emerge (e.g. prolonged corticosteroid exposure) (evidence category D).

### **8.3 Management**

Optimal bone health and management of osteoporosis is best achieved by utilising the expertise of a variety of CF team members, including dietitians, respiratory physicians and physiotherapists, and consultation with other specialists (e.g. an endocrinologist). Aspects that should be assessed and monitored include dietary intake, nutritional status, vitamin D status, risk factors and frequency of DXA scanning.

The management of reduced BMD includes anti-bone resorptive medication and a diet high in calcium. Bisphosphonates have been observed to be effective in improving the BMD of adults with CF [338-340] (evidence category B), but their use in children with CF has not been established [330]. All aspects regarding routine nutritional management (see section 5) should be reviewed in order to optimise nutritional status, macro- and micronutrient intakes and PERT (evidence category D). In addition to optimising calcium intake, serum 25-hydroxyvitamin D levels need to be monitored regularly and vitamin D supplementation altered, if necessary, to achieve optimum levels (see section 4.3.6) [330]. Ideally, supplementation with cholecalciferol (vitamin D<sub>3</sub>) is recommended for valid serum monitoring as ergocalciferol (vitamin D<sub>2</sub>) is not reliably measured in all 25-hydroxyvitamin D<sub>3</sub> assays [341].

In the absence of evidence for CF-specific recommendations [330], calcium intake for all individuals with CF should be at least the age-specific Australian RDIs [170] (evidence category D) (see section 4.4.3). Calcium supplementation may be required to achieve this level of intake.

Recommendations for calcium intake in those with low BMD in other population sub-groups suggest up to 1500 mg per day be achieved [213, 214] (evidence category D). Trials of calcium supplementation in non-CF populations show an increase in BMD of the order of one to two percent and a reduction in the risk of fracture [342, 343]. Calcium supplementation should commence when medications (e.g. bisphosphonates, vitamin D) for low BMD are prescribed [213] (evidence category D).

Similar to recommendations for those with osteoporosis in the general population, weight-bearing exercise may assist in minimising the effects of bone disease [330] (evidence category D). Impact or manipulative therapies, such as percussion, chiropractic or osteopathic treatments, may need to be altered in order to decrease the risk of fractures. Occupational, sporting and leisure activities of individuals with osteoporosis should be reviewed in order to reduce the risk of falls and other types of impact that may result in fracturing (evidence category D).

## **Recommendations**

**1. BMD should be assessed periodically in individuals with CF who are more than eight years of age (C).**

**2. Nutritional management for optimising BMD in individuals with CF includes:**

- **adequate calcium intake to at least the age-specific RDI for all individuals**
- **a calcium intake of 1500 mg/day for those with low BMD**
- **the use of calcium supplements to meet target intakes**
- **supplementation of vitamin D as required to achieve a serum 25-hydroxyvitamin D level of at least 50 nmol/L**
- **a diet adequate in energy to meet nutritional status objectives and the RDIs for all micronutrients, and;**
- **strategies to prevent or treat malnutrition.**

**(D)**

## **9. Pregnancy**

### **9.1 Pregnancy outcome**

Nutrition plays an important role prior to conception and during pregnancy in women with CF [11] (evidence category D). Positive outcomes for both the woman with CF and her infant have been associated with better nutritional status, indirectly through better pulmonary function prior to pregnancy and maintenance of lung function during pregnancy [344, 345] (evidence category C), and directly through pancreatic sufficiency, appropriate weight for height at conception and weight gain of at least 10 kg throughout the pregnancy [346, 347] (evidence category C). A multidisciplinary team approach to respiratory, nutritional and obstetric care is recommended in order to optimise the outcomes of pregnancy in women with CF [346-348] (evidence category D). Survival rates of women with CF do not appear to be adversely affected by pregnancy [349] (evidence category B).

### **9.2 Nutritional assessment & counselling**

#### **9.2.1 Overview**

Research evidence regarding optimum nutritional management of the reproductive health of women with CF is limited. Actual intake would need to meet both the increased dietary requirements for CF, as outlined in section 4, and those for pregnancy, as detailed by the NHMRC [170] (evidence category B). A comprehensive assessment prior to conception provides the opportunity to optimise the nutritional status of a woman with CF. In situations where the pregnancy is unplanned, nutritional counselling is required as soon as possible.

The nutritional assessment of a woman with CF who is planning a pregnancy or who is already pregnant should include the following:

- weight and height measurements, BMI and advice regarding expected weight gain (>10 kg)
- a diet history, quantitative assessment of dietary intake and counselling to address the requirements of pregnancy combined with CF, including information regarding the availability of oral and enteral supplementation if needed
- a review of PERT (see section 5.2)
- adjustment of fat-soluble vitamins to normalise serum levels, if necessary (see section 4.3)
- supplementation of folate and, if necessary, iron (see section 4.4.2)
- general advice regarding food safety
- review of blood glucose levels (see section 7)
- advice regarding nausea, vomiting, GOR and constipation, if applicable, and
- information about lactation.

#### **9.2.2 Vitamin A**

Serum vitamin A levels of women with CF who are pregnant should be reviewed no less frequently than at the beginning of each trimester as a relationship between the incidence of birth defects and excessive doses has been observed in a non-CF study [350] (evidence category C). Supplementation should be <10 000 IU/day if serum vitamin A levels are low, or normal, and ceased when levels are elevated [10, 11] (evidence category D).

### **9.2.3 Folate**

Regardless of CF, all women who are planning to conceive and whose pregnancy is in the first trimester should consume a folate-rich diet [351] and supplement at a dose of 0.5 mg/day. If there is a family history of neural tube defects then supplementation should be five mg of folic acid/day [170].

### **9.2.4 Food safety**

As with the general population, all women with CF who are planning a pregnancy, or as soon as possible after pregnancy is confirmed, should be informed about correct food handling procedures in order to minimise the risk of infections (e.g. listeriosis, toxoplasmosis and salmonellosis) and mercury poisoning from fish, which are potentially harmful to the foetus [352] (evidence category D) [353].

### **9.2.5 Gestational CFRD**

During pregnancy, a woman with CF is at greater risk of developing diabetes than the general population as a result of individuals with CF having compromised beta cell function [158] (evidence category D). Although there is limited information regarding the incidence and prevalence of elevated blood glucose levels in pregnant women with CF, USA consensus guidelines [158] (evidence category D) suggest conducting a 75 gm OGTT prior to conception, or a 100 g OGTT at the time pregnancy is confirmed, and repeating the test during weeks 20-24 and weeks 30-34. Monitoring of fasting and post-prandial blood glucose levels in pregnant women with CF is also advisable [158, 354] (evidence category D).

Optimum control of blood glucose levels during pregnancy is warranted as women with CFRD who are pregnant have an increased risk of maternal morbidity [158, 320] (evidence category D). Treatment for elevated blood glucose levels in pregnant women is insulin, as for CFRD (see section 7), in conjunction with meeting nutritional requirements for pregnancy. All women with CF who are pregnant should be promptly referred to an endocrinologist in order to optimise blood glucose control throughout the pregnancy. Tight control of blood glucose levels during pregnancy is recommended, with ideal fasting blood glucose levels <5.8 mmol/l, 1 hour post prandial blood glucose levels <10.6 mmol/l and two hour post prandial blood glucose levels <9.2 mmol/l [158] (evidence category D).

### **9.2.6 Additional nutritional support**

Women with CF are likely to require additional nutritional support during pregnancy in order to minimise the potential negative effects of chest exacerbations, hospital admissions and deterioration in lung function on appetite and dietary intake. Helpful literature for women with CF who are pregnant can be accessed on-line at [www.cftrust.org.uk](http://www.cftrust.org.uk).

Frequent clinic reviews (as often as every four to six weeks) from conception or confirmation of the pregnancy, enable weight, PERT and lung function to be monitored closely. A weight gain of at least 10 kg throughout pregnancy in women with CF has been associated with positive outcomes [346, 347] (evidence category C). This weight gain compares favourably with the average total of 12.5 kg in pregnant women who do not have CF. If weight gain is inadequate, then nutritional supplementation may be necessary, either orally or enterally [355] (evidence category D) (see sections 5.5 & 5.7).

Throughout the pregnancy, specific and practical advice from a dietitian with expertise in CF should be provided. Factors to address in addition to the standard nutritional issues related to CF

include pregnancy related nausea and vomiting, GOR, constipation and nutritional support [11, 356] (evidence category D).

### **9.2.7 Lactation**

As with all pregnancies, the mother's preferred method of feeding her infant should be supported. There is no contraindication to breastfeeding for a mother with CF, provided an adequate intake of energy can be maintained [11] (evidence category D). It is interesting to note that the sodium content of breast milk in women with CF is normal [345].

Nutritional counselling pre-conception and during pregnancy should alert the woman with CF to the increased energy and nutrient demands of breastfeeding [170] (evidence category B). Weight should be monitored during lactation and adjustments to oral intake made if necessary. The initial period of establishing lactation may be adversely affected by complications resulting from delivery, including the need for additional physiotherapy, intravenous antibiotics, caesarean section or pneumothorax [11] (evidence category D). It is often helpful to involve the woman's partner and/or family in counselling sessions in order to enhance the likelihood of success with breastfeeding, maintenance of optimal nutritional status and completion of medical treatments associated with CF. Community support for breastfeeding can be sought from the Australian Breastfeeding Association ([www.breastfeeding.asn.au](http://www.breastfeeding.asn.au)) and from La Leche League in NZ ([www.lalecheleague.org.nz/](http://www.lalecheleague.org.nz/)).

### **Recommendations**

- 1. Provide preconception and early pregnancy nutritional assessment and counselling, including advice regarding food safety (D).**
- 2. Review glucose tolerance, gestational CFRD status, iron levels, vitamin A status and supplementation (D).**
- 3. Supplement with 0.5 mg/day of folic acid in the preconception period and throughout the first trimester (A).**
- 4. Aim to achieve a weight gain of at least 10 kg during pregnancy (C).**
- 5. Ensure close liaison between the specialist CF centre staff and obstetric team to ensure effective and consistent management of both CF and pregnancy (D).**

## 10. Lung transplantation

### 10.1 Impact of nutritional status

Lung transplantation is a treatment option for some individuals with end stage CF. Actuarial survival for adult lung transplant recipients with CF, is reported as one year 78.6%, three years 63%, five years 52.9%, seven years 44.9% and 10 years 34.1% [357] (evidence category C). Prior to an individual with end stage CF being listed for lung transplantation, numerous aspects need to be assessed, including pulmonary function, rate of declining spirometry values, age, BMI, recent weight fluctuations, pancreatic function, CFRD, osteoporosis, GOR, quality of life and patient and physician choice. Extremes of body weight, BMI and lean body mass have been demonstrated to negatively affect lung transplant outcome [358-361] (evidence category C). International guidelines recommend that individuals with a weight of <70% of IBW should strive to gain weight, and those whose weight is >130% IBW should aim to lose weight, to be eligible for transplantation [362] (evidence category D). These criteria equate to BMIs of approximately 16kg/m<sup>2</sup> and 29kg/m<sup>2</sup> respectively, if 100%IBW equates to a BMI of 22kg/m<sup>2</sup>.

When an individual with CF is registered on the lung transplantation waiting list it is important to continue to optimise nutritional status for the best possible outcome. Prior to lung transplantation, individuals with CF with end-stage lung disease are at risk of significant weight loss as energy expenditure is raised, secondary to pulmonary sepsis, declining respiratory function and the increased work of breathing associated with infective exacerbation [363, 364] (evidence category C). Maintenance of lean body mass should be a priority and goals should focus on optimising nutritional status and exercise capacity [365] (evidence category D). The option of transplantation may provide an incentive for the individual with CF to make additional efforts to optimise their nutritional status. Aggressive nutritional support may be required to counteract the rise in requirements in end stage CF. In general, however, transplantation should not be delayed while attempts are made to increase weight [360] (evidence category C).

### 10.2 Nutritional management prior to lung transplantation

Relevant nutritional information provided by the dietitian from the referring CF centre enhances the full nutritional assessment performed by the lung transplant dietitian, prior to the individual with CF being placed on the transplant waiting list, as current data can be compared with the individual's past history. Factors taken into consideration include:

- anthropometry and body composition, such as height, weight, BMI, skinfold measurements, DXA and bioelectrical impedance analysis, where available
- nutritional history, including appetite, nausea, vomiting, dietary intake, mode of intake (oral, enteral or parenteral), supplements, PERT, diarrhoea, constipation, weight changes and comorbidities
- biochemistry, particularly full blood count, urea and electrolytes, levels of fat-soluble vitamins and random blood glucose levels
- physical parameters, such as muscle tone, fat stores, oedema, weakness and fatigue, and
- social and emotional issues affecting adherence to dietary advice.

The aims of nutritional management prior to lung transplantation are to:

- optimise dietary intake, using high energy/protein oral supplements, if indicated
- achieve a BMI of between 17 and 27 kg/m<sup>2</sup>, ideally 20 to 25 kg/m<sup>2</sup>
- provide enteral feeding if oral intake alone is insufficient in meeting nutritional requirements
- optimise PERT

- provide all required supplements (vitamins, sodium and calcium), and
- optimise management of co-morbidities if present (e.g. CFRD).

### ***10.3 Nutritional management post-lung transplantation***

In the immediate post-operative period, maintenance of adequate nutritional intake is a priority. Nutrient needs are increased in order to offset catabolism secondary to surgery and anti-rejection medication [366] (evidence category D). In view of the lack of CF-specific recommendations, energy and protein requirements post-lung transplantation are based on recommendations for general surgical and other types of transplant patients. Immediate post-operative energy requirements are estimated to be 1.35–1.75 times basal energy expenditure and protein needs are thought to be 1.3–2.5 g protein/kg/body weight [367] (evidence category C).

Diet therapy post-lung transplantation can usually commence one to two days post-operatively with an oral liquid diet if the individual has been extubated. Intake can advance as tolerated to a regular diet for CF, with accompanying PERT [365, 366] (evidence category D). Some individuals regain their appetite and eat well soon after transplantation, as breathing becomes easier, taste sensations improve, bowel function normalises and mobility improves. However, others may experience anorexia and poor oral intake due to post-transplantation medications, taste changes, constipation, nausea and vomiting [366] (evidence category D). Supplementary enteral feeding should be initiated if oral intake is insufficient, if the individual is unable to commence an oral diet by three to four days post-operatively or if longer-term intensive care and ventilation is required.

Upon discharge from hospital after lung transplantation, routine nutritional management should be re-established (see section 5). After lung transplantation, energy requirements decrease, as the work of breathing lessens and infective exacerbations are fewer, and appetite improves, due to the effects of anti-rejection medications and improvement in overall well-being. Dietary fat and energy intake may need to be reduced to a moderate amount in order to maintain a BMI of between 20 and 25 kg/m<sup>2</sup> in adults. Pancreatic enzyme dosage will require adjustment relative to changes made to the diet (see section 5.2). Some individuals will require additional dietary counselling to normalise eating habits and achieve a varied diet, particularly those who have relied heavily on oral supplements or enteral feeding prior to transplant.

Patients who have relied on supplementary enteral nutrition via a gastrostomy tube prior to lung transplantation can often reduce the use of enteral nutrition as oral intake increases and nutritional status becomes adequate. Gastrostomy removal should be discussed between the patient, CF team and lung transplant team and assessed on an individual basis. Ideally, removal should only be planned when a BMI within the healthy weight range has been achieved, and maintained without supplementary enteral nutrition. It is suggested that weight maintenance or continued gain without enteral nutrition should be demonstrated for at least three months before removal take place. Spontaneous closure of gastrostomy tract after removal of the tube has been demonstrated in one study to be significantly related to the duration of gastrostomy *in situ* prior to renal transplant, with spontaneous closure occurring in gastrostomies placed less than one year prior to the transplant [368] (evidence category B). Davies and colleagues [368] recommended formal closure of all gastrostomies that have been *in situ* for more than one year. No studies in CF lung transplant recipients have been published, although clinical experience would support formal closure in patients with longstanding gastrostomies.

Post-lung transplantation, vitamin requirements are often no longer elevated. Vitamin A and E levels have been observed to be significantly higher post-lung transplantation, even after supplementation ceased [369] (evidence category C). The decrease in pulmonary exacerbations, altered absorption, drug interactions, impaired retinol metabolism or increased hepatic synthesis of retinol binding protein are possible factors influencing post-lung transplantation vitamin levels

[155, 369] (evidence category C). Regular monitoring of vitamin levels will indicate when supplementation can be reduced or ceased.

#### ***10.4 Impact of post-lung transplantation co-morbidities***

Medical complications post-transplantation include graft rejection and infection. Medications used to prevent and treat these complications, such as antibiotics and anti-fungal medications, can have debilitating side effects, namely taste changes, nausea, vomiting and diarrhoea. Post-transplantation infection and rejection can cause energy and protein requirements to be increased, thus, nutritional support should be tailored to each individual during these times.

The post-transplant immunosuppressive regimen, which includes high doses of prednisolone and tacrolimus, places patients at risk of new onset of, or exacerbation of, existing CFRD, secondary to insulin resistance and insulin deficiency [2, 366] (evidence category D). Insulin is usually required, at least in the short-term, and nutritional management should be tailored to the individual's preferences, particularly if oral intake is poor (see section 7). Steroids and other medications that are required post-transplant may also exacerbate osteoporosis, gastrointestinal tract motility disorders and renal dysfunction.

Osteoporosis that occurs post-lung transplantation appears to be more severe than that associated with heart, kidney, liver or bone marrow transplants [332] (evidence category C). Pathogenesis of osteoporosis post-transplantation appears to be multifactorial, with cumulative steroid doses being the major contributing factor. Most individuals with osteoporosis require anti-bone resorptive medication and a diet high in calcium. Adequate vitamin D levels and weight-bearing exercise will also assist in minimising the effects of the disease (see section 8).

Gastrointestinal complications, particularly GOR and constipation, are common post-lung transplantation [370] (evidence category C). The aetiology of post-lung transplant-related GOR is poorly understood, with possible causes being vagal injury, delayed gastric emptying, oesophageal dysmotility and oesophageal sphincter relaxation. Section 6.5 provides a summary of management strategies for GOR.

Constipation is common, particularly immediately post-lung transplantation. Prevention and early treatment of constipation is required to avoid the more serious complication of DIOS. Individuals with a history of previous major abdominal surgery, meconium ileus in infancy or DIOS require close monitoring as they are at greater risk of developing post-transplantation DIOS [371] (evidence category C). Counselling regarding a high fibre diet (see section 4.2.5) and adequate sodium and fluids (see section 4.4.1) should be provided.

Organ transplant recipients are at high risk of drug-nutrient interactions due to multiple medication regimens. In particular, grapefruit juice should be avoided as this interferes with the absorption of some immuno-suppressive drugs [372] (evidence category A), namely cyclosporin and tacrolimus. Cyclosporin is highly lipophilic, and sub-optimal enteral absorption may account for low bioavailability in individuals with CF [373] (evidence category B). Lung transplant physicians may recommend one to two low dose pancreatic enzyme capsules be administered with each dose of medication to facilitate absorption. However, PERT may have no effect on cyclosporin bioavailability and higher doses of immunosuppression drugs may be needed by individuals with pancreatic insufficiency in order to achieve therapeutic concentrations [373] (evidence category B).

Numerous other nutritional factors that need to be considered post-lung transplantation include:

- food safety, as immunosuppression therapy places individuals at higher risk of food borne illness [353]

- avoidance of large amounts of alcohol, as this may cause dehydration, and avoidance of all alcohol if contraindicated by liver disease or interference with drug absorption
- magnesium supplementation if levels are reduced due to the use of diuretics and immunosuppressive medications
- adequate hydration (up to 3-4 L/day, if required) as renal function may be adversely affected by immunosuppressive medications
- optimum blood glucose control in those with diabetes or hyperglycaemia
- a reduction in potassium intake if immunosuppressive medications cause potassium retention, which is particularly hazardous in individuals with low body weight, and
- increased nutritional requirements with rejection and intercurrent illnesses.

## **Recommendations**

### ***Pre-lung transplantation management***

- 1. Optimise nutritional intake, using high energy/protein oral supplements as required (D).**
- 2. Aim to attain a BMI of 17-27 kg/m<sup>2</sup>, ideally 20-25 kg/m<sup>2</sup>(D).**
- 3. Provide enteral tube feeding if oral intake alone is insufficient for meeting increased requirements (D).**
- 4. Optimise PERT (D).**
- 5. Provide all required supplements (e.g. vitamins, sodium and calcium) (D).**
- 6. Optimise management of co-morbidities if present (e.g. CFRD) (D).**
- 7. Ensure liaison occurs between the referring CF centre dietitian and the lung transplant unit dietitian regarding all relevant nutritional issues (D).**

### ***Post-lung transplantation management***

- 1. Optimise nutritional intake using high energy/protein oral supplements as required (D).**
- 2. Prevent/treat constipation, particularly in the early post-transplant period, by encouraging adequate fluid, sodium and PERT (D).**
- 3. Monitor pre- and post-prandial blood glucose levels particularly when high dose steroids are being administered (D).**
- 4. Aim for BMI 20–25 kg/m<sup>2</sup> in the long-term (D).**
- 5. Provide dietetic counselling regarding sensible healthy eating, moderate fat intake and adjustments in PERT after acute recovery phase (D).**
- 6. Encourage adequate calcium intake (D).**
- 7. Monitor fat-soluble vitamin levels and adjust supplement intake accordingly (C).**
- 8. Encourage safe food handling and avoid high-risk foods (D).**
- 9. Monitor magnesium levels and discuss supplementation with transplant team as necessary (D).**
- 10. Continue close communication between CF centre and transplant unit (D).**

## **11. Implementation & evaluation of the Guidelines**

### ***11.1 Implementation plan***

The Guidelines will be made available to target users via the following avenues (subject to confirmation):

- publication on the websites of the professional associations of the target users, and of Cystic Fibrosis Australia
- notification by mail or email to:
  - Dietitians via newsletters of their professional associations, and through the CF clinics in Australia and New Zealand known to the writing group
  - Other health professionals working in CF, through the clinics in Australia and New Zealand known to the writing group.

If funding is available to support printing and distribution costs, printed versions of the Guidelines will be circulated to Australian and New Zealand dietitians working in the CF clinics known to the writing group.

If resources are obtainable, a workshop for dietitians will be held at the annual meeting of the DAA CF Interest Group, addressing the Guidelines' content, recommendations and implementation into clinical practice.

### ***11.2 Evaluation plan***

The Guidelines will be evaluated via a survey of dietetic practice and nutritional management of CF in Australia and New Zealand, similar to the 2005 survey outlined in section 1.6, with the addition of items specifically addressing aspects of the Guidelines. It is anticipated that this survey would be conducted not less than one year after finalisation of the Guidelines.

### ***11.3 Recommendations for research***

Further research is required in order to make recommendations regarding:

1. Optimal serum levels of vitamin A and the safe upper limit for vitamin A supplementation (section 4.3.5)
2. The usefulness of the vitamin E:total lipid ratio for assessing vitamin E status and the safe upper limit for vitamin E supplementation (section 4.3.7)
3. Appropriate doses for vitamin K supplementation (section 4.3.8)
4. Appropriate doses for iron supplementation (section 4.4.2)
5. Whether additional calcium is routinely required in CF compared with the general population (section 4.4.3)
6. The role of antioxidant supplementation in CF (section 4.5.1)
7. The affect of altering dietary fat composition on lung disease (section 4.5.2)
8. The role of probiotics in CF (section 4.5.3)
9. Whether fat absorption can be normalised in CF by further manipulation of PERT (section 5.2.4)
10. The optimal PERT dosing strategy for polymeric enteral tube feeding (sections 5.2.4 and 5.7.6)
11. The role of dietary manipulation in individuals with CF and GOR (section 6.5)
12. The impact of enteral nutrition regimens and delivery route on GOR in CF (section 6.5)
13. The optimal strategy for screening for CFRD (section 7.2)

## Appendices

### Appendix 1: National dietetic service provision within CF facilities across Australia, 2004

Table 1: UK recommendations for suggested number of whole time equivalent staff required for every 50 patients on full care [39, 121]

<i>Staff Member</i>	<i>Local Clinic (&lt; 50 patients)</i>	<i>Specialist Paediatric Centre</i>	<i>Specialist Adult Centre</i>
Consultant 1	0.5	0.5	0.5
Consultant 2	Nil	0.2–0.3	0.2–0.3
Staff Grade	Nil	0.4	0.6
CF Sp. R	Nil	0.5	0.5
CF Nurse	1.0	1.0–1.5	1.0–1.5
Physiotherapist	1.0-2.0	2.0	2.0
<b>Dietitian</b>	<b>0.4</b>	<b>0.4</b>	<b>0.4</b>
Social Worker	0.4	0.4	0.4
Psychologist	0.4	0.4	0.4
Secretary	0.5	1.0	1.0
Data clerk	Nil	0.1	0.1
Pharmacist	0.2	0.3	0.3

In 2004, the DAA CF Interest Group surveyed all members across Australia, obtaining demographic information about the number of patients attending CF facilities and the full time equivalent dietetic service provision. Table 2 summarises the service provided by Dietitians compared with unit size. The current Australian Dietetic staffing resources allocated nationally is also compared to UK recommended levels [32].

Table 2: Australian Dietetic staffing resources allocated nationally to CF facilities compared to UK recommendations [32]

Hospital	Type of pts	Estimated total pt numbers	Dietitian FTE	FTE Per 50 pts	%UK recommendation
RCH, Melb	Chn/Adol	350	1.4	0.2	50%
Westmead	Chn/Adol	320	0.6-0.8	0.11	28%
Sydney Chn	Chn/Adol	120	0.3	0.13	33%
RCH, Bris	Chn/Adol	300	0.6	0.10	25%
JHH	Chn/Adol	65	0.2	0.15	38%
PMH, Perth	Chn/Adol	170	0.4-0.5	0.13	33%
Adel Chn	Chn/Adol	160	0.3	0.1	25%
Gold Coast	Chn/Adol	30	<0.1	0.17	43%
ACT	Chn/Adol	30	<0.1	0.17	43%
MMC	Chn/Adol/adults	111	0.5	0.23	58%
JHH	Adults	35	0.1	0.14	35%
Townsville	Chn/Adol/adults	25	<0.1	0.2	50%
Hobart	Chn/Adol/adults	49	<0.1	0.1	25%
Prince Charles, Bris	Adults	210	1.1	0.26	65%
RPA	Adol/adults	?	?	?	
Alfred	Adults	200	0.8	0.20	50%
St Vincents, Sydney	Adol/adults	60	0.1-0.2?	0.13	33%
				Range: 0.1-0.26	Range: 25-65%
				Mean: 0.16	Mean: 40%

The mean FTE per 50 CF patients across all Australian CF Units is 0.16 FTE/50 patients, based on 1.0 FTE= 38hrs/week.

This is equivalent to 6.1hrs per 50 patients (7.3 minutes per patient).

The overall service provision ranges 0.1–0.26 FTE/50 patients.

UK recommendations published in 2001 suggest 0.4 FTE/50 patients, therefore Australian CF Units provide, on average, 40% of the recommended Dietetic staffing levels for CF Care (range 25–65 % of recommendations).

Currently, all National Australian CF Services are under staffed in the provision of adequate minimum Dietetic service provision according to the UK CF Trust recommendations.

## Appendix 2: Australian Guidelines for Pancreatic Enzyme Replacement Therapy

<b>Infants</b>
<ul style="list-style-type: none"> <li>• 500-1000 U lipase/g of dietary fat</li> <li>• Commence with the minimum dose (e.g. 2,500 units lipase/breast feed or 120ml infant formula)</li> <li>• Titrate dose according to weight gain and bowel signs</li> </ul>
<b>Children and Adults</b>
<ul style="list-style-type: none"> <li>• 500-4000 U lipase/g of dietary fat</li> <li>• Maximum dose of 10,000 U lipase/kg body weight/d</li> <li>• Aim for lowest effective dose</li> <li>• Use individual approach</li> <li>• Distribute the enzymes throughout the day in alliance with the fat content of food and drinks consumed</li> <li>• Monitor weight gain, growth and bowel signs</li> <li>• Patients should be encouraged to discuss PERT with clinic staff before increasing dose</li> </ul>
<b>Before PERT dose is increased evaluate the following:</b>
<b>Distribution</b>
<ul style="list-style-type: none"> <li>• Check that PERT is correctly distributed over the day's meals based on the fat content of individual meals, snacks and fluids, e.g. milk</li> </ul>
<b>Administration</b>
<ul style="list-style-type: none"> <li>• Capsules should be swallowed whole or the granules inside the capsules mixed with an acidic fruit puree e.g. apple. Granules should not be chewed</li> <li>• Enzymes should be taken before and/or during meal or snack. Enzymes are effective for 30 min after consumption. Therefore, additional enzymes are required of eating or drinking milk (or infant formula) 30 min after the first dose</li> </ul>
<b>Storage</b>
<ul style="list-style-type: none"> <li>• Store capsules in an airtight container, in a cool, dry place</li> <li>• Check the enzymes capsules have not exceeded the expiry date</li> </ul>
<b>Adherence</b>
<ul style="list-style-type: none"> <li>• Administer PERT with all meals, snacks and fluid containing fat</li> <li>• Avoid increasing the dose if adherence is poor</li> <li>• Develop strategies to improve adherence, particularly at school</li> </ul>
<b>Efficacy</b>
Implement and evaluate the following if PERT appears to be ineffective:
<ul style="list-style-type: none"> <li>• Measure faecal fat excretion (%FFE)</li> <li>• Increase PERT dose by small increment but avoid exceeding the maximum 'safe' dose of 10,000 U lipase/kg/d</li> <li>• Consider use of adjunctive therapies e.g. H<sub>2</sub> blockers, synthetic prostaglandins</li> <li>• Refer to gastroenterologist for review of PERT and/or GI investigation</li> </ul>
<b>Before using acid suppressing agents</b>
<ul style="list-style-type: none"> <li>• Document %FFE and usual PERT intake and distribution</li> <li>• Add adjunctive agent</li> <li>• Repeat measurement of %FFE and assessment of PERT intake and distribution</li> </ul>

Reproduced from Anthony, H., Collins C. E. Davidson, G. et al. *Pancreatic enzyme replacement therapy in cystic fibrosis: Australian guidelines*. Journal of Paediatrics and Child Health, 1999. 35(2): 125-9 with permission.

**Appendix 3: Pancreatic enzyme products available in Australia**

<b>Preparation</b>	<b>Company</b>	<b>Lipase (U)</b>	<b>Protease (U)</b>	<b>Amylase (U)</b>
Creon 5000	Solvay	5 000	300	4 000
Cotazym-S-Forte	Organon	10 000	750	7 700
Creon 10 000	Solvay	10 000	600	8 000
Creon Forte (Creon 25000)	Solvay	25 000	1 000	18 000
Panzytrat	Technipro	25 000	1 256	22 500

**Appendix 4: Recommendations for the use of PERT with enteral tube feeding**

Two options for calculating PERT doses for enteral tube feeding, based on the use of a polymeric formula and the Australian PERT Guidelines (Appendix 2 and [30]).

<b>Plan A</b>	<b>Plan B</b>
<p><b>Step 1</b> Estimate the amount of fat in the total volume of the feed to be delivered</p>	<p>Estimate the amount of fat to be delivered every three hours</p>
<p><b>Step 2</b> Divide the total amount of fat by the individual's recommended pancreatic enzyme dose to determine the number of capsules required for the whole feed</p>	<p>Divide this amount of fat by the individual's recommended pancreatic enzyme dose to determine the number of capsules required every three hours</p>
<p><b>Step 3</b> Possible dosing options: <i>Single:</i> take one dose, as determined in step 2, prior to commencing the feed (14)  <i>Double:</i> take 50% of the dose determined in step 2 prior to going to sleep, if more than one hour has lapsed, or whenever voluntarily away through the night (14)  <i>Multiple:</i> if feeding for longer than six hours, take additional 50% doses if voluntarily awake at any time after this</p>	<p>Possible dosing options: <i>Single:</i> take one dose, as determined in step 2, prior to commencing the feed  <i>Double:</i> as per single option plus take the same dose again prior to going to sleep, if more than one hour has elapsed, or whenever voluntarily awake through the night  <i>Multiple:</i> if feeding for longer than six hours, take additional doses, as determined in step 2, if voluntarily awake at any time after this</p>

Reproduced from Stapleton, D.R., Anthony, H. et al, *Implementing the Australian pancreatic enzyme replacement therapy guidelines for cystic fibrosis*. Australian Journal of Nutrition and Dietetics, 1999. **56**(2): 91-96 with permission.

### ***Appendix 5: Behavioural change***

The challenge in health promotion is to translate a theory-based model into a program that includes a series of learning activities that will influence behaviour change [374]. Following is a list of program strategies that numerous studies and reviews [102, 374-380] recommend for use in health education programs targeting children. The strategies are based on social learning theory constructs and are useful for teaching the behaviours that are required and how to develop them.

1. Provide clear information in developmentally appropriate ways.
2. Involve the family unit.
3. Encourage family members to reinforce the advice provided & the appropriate behaviours exhibited.
4. Establish concrete behavioural goals.
5. Allow the individual to determine and participate in appropriate aspects of treatment.
6. Develop mastery over treatment skills.
7. Introduce record keeping in order for the individual to self-monitor adherence and progress with behavioural goals and to assume more self-responsibility and awareness. Records are also a useful basis for feedback from the health-care provider.
8. Provide interim follow-up through telephone calls and checking of self- monitoring records.
9. Implement a structured reward system, in which the individual chooses the rewards.
10. Develop problem-solving skills.
11. Provide opportunities for actual experience and participation.

## ***Appendix 6: Writing group declarations***

Writing Group potential conflict of interest and funding declarations (2001-2005).

Colleen Ash	Conference attendance, 2005	Solvay Pharmaceuticals
Clare Collins	nil	
Christie Graham	nil	
Karen Herd	Conference attendance 2003	Nutricia Australia
Susannah King	Solvay Travel Scholarship, 2004*	Solvay Pharmaceuticals
	Conference attendance 2002	Nutricia Australia
Angela Matson	Solvay Travel Scholarship, 2001*	Solvay Pharmaceuticals
Denise Stapleton**	nil	
Evelyn Volders	nil	

\* Travel scholarship awarded annually by competitive process, offered within the Australian CF health professional community, assessed and judged by a panel of clinical experts in this field.

\*\* Employed as project officer October 2004 – June 2005 to collate guideline materials and evidence for early drafts.

## References

1. Cystic Fibrosis Australia, *Cystic fibrosis in Australia and New Zealand 2002: Annual Report from the Australasian Cystic Fibrosis Data Registry*. 2004, Cystic Fibrosis Australia: Sydney.
2. Yankaskas, J.R., B.C. Marshall, B. Sufian, R.H. Simon, and D. Rodman, *Cystic fibrosis adult care: consensus conference report*. Chest, 2004. **125**(1 Suppl): 1S-39S.
3. The Victorian Clinical Standards Advisory Group on Cystic Fibrosis, *Quality of care guidelines for cystic fibrosis care. Recommendations of the Victorian Clinical Standards Advisory Group on Cystic Fibrosis*. 1999: Melbourne.
4. Robinson, P., *Cystic fibrosis: paediatric origins of adult lung disease*. Thorax, 2001. **56**: 237-241.
5. Doull, I.J.M., *Recent advances in cystic fibrosis*. Archives of Disease in Childhood, 2001. **85**: 62-66.
6. Phelan, P. and E. Hey, *Cystic fibrosis mortality in England and Wales and in Victoria, Australia 1976-80*. Archives of Disease in Childhood, 1984. **59**: 71-3.
7. Mahadeva, R., K. Webb, R.C. Westerbeek, et al., *Clinical outcome in relation to care in centres specialising in cystic fibrosis: cross sectional study*. BMJ, 1998. **316**(7147): 1771-5.
8. Borowitz, D., R.D. Baker, and V. Stallings, *Consensus report on nutrition for pediatric patients with cystic fibrosis*. Journal of Pediatric Gastroenterology and Nutrition, 2002. **35**(3): 246-59.
9. Pencharz, P.B. and P.R. Durie, *Pathogenesis of malnutrition in cystic fibrosis, and its treatment*. Clinical Nutrition, 2000. **19**(6): 387-94.
10. Sinaasappel, M., M. Stern, J. Littlewood, et al., *Nutrition in patients with cystic fibrosis: a European Consensus*. Journal of Cystic Fibrosis, 2002. **1**: 51-75.
11. UK Cystic Fibrosis Trust Nutrition Working Group, *Nutritional management of cystic fibrosis*. 2002, Cystic Fibrosis Trust: Bromley, Kent, UK.
12. WHO, ICF(M)A, and IACFA, *Services for adults with cystic fibrosis: Report of a joint WHO/ICF(M)A/IACFA meeting, The Hague, The Netherlands, 7-8 June, 1999*. Journal of Cystic Fibrosis, 2002. **1**: 103-109.
13. Sharma, R., V.G. Florea, A.P. Bolger, et al., *Wasting as an independent predictor of mortality in patients with cystic fibrosis*. Thorax, 2001. **56**(10): 746-50.
14. Beker, L.T., E. Russek-Cohen, and R.J. Fink, *Stature as a prognostic factor in cystic fibrosis survival*. Journal of the American Dietetic Association, 2001. **101**(4): 438-42.
15. Corey, M., F.J. McLaughlin, M. Williams, and H. Levison, *A comparison of survival, growth and pulmonary function in patients with cystic fibrosis in Boston and Toronto*. Journal of Clinical Epidemiology, 1988. **41**(6): 583-591.
16. Richardson, I., I. Nyulasi, K. Cameron, M. Ball, and J. Wilson, *Nutritional status of an adult cystic fibrosis population*. Nutrition, 2000. **16**(4): 255-9.
17. Pencharz, P.B. and P.R. Durie, *Nutritional management of cystic fibrosis*. Annual Review of Nutrition, 1993. **13**: 111-136.
18. Peters, S.A. and C.J. Rolles, *Vitamin therapy in cystic fibrosis - a review and rationale*. Journal of Clinical Pharmacy and Therapeutics, 1993. **18**(1): 33-8.
19. Constantini, D., R. Padoan, L. Curcio, and A. Giunta, *The management of enzymatic therapy in cystic fibrosis patients by an individualized approach*. Journal of Pediatric Gastroenterology and Nutrition, 1988. **7 Suppl 1**: S36-9.
20. Levy, L.D., P.R. Durie, P.B. Pencharz, and M.L. Corey, *Effects of long-term nutritional rehabilitation on body composition and clinical status in malnourished children and adolescents with cystic fibrosis*. Journal of Pediatrics, 1985. **107**(2): 225-230.
21. Shepherd, R.W., T.L. Holt, B.J. Thomas, et al., *Nutritional rehabilitation in cystic fibrosis: controlled studies of effects on nutritional growth retardation, body protein turnover, and course of pulmonary disease*. Journal of Pediatrics, 1986. **109**(5): 788-94.
22. Steinkamp, G. and H. Van Der Hardt, *Improvement of nutritional status and lung function after long-term nocturnal gastrostomy feedings in cystic fibrosis*. Journal of Pediatrics, 1994. **124**: 244-249.
23. Walker, S.A. and D. Gozal, *Pulmonary function correlates in the prediction of long-term weight gain in cystic fibrosis patients with gastrostomy tube feedings*. Journal of Pediatric Gastroenterology and Nutrition, 1998. **27**(1): 53-6.
24. Williams, S.G., F. Ashworth, A. McAlweenie, S. Poole, M.E. Hodson, and D. Westaby, *Percutaneous endoscopic gastrostomy feeding in patients with cystic fibrosis*. Gut, 1999. **44**(1): 87-90.

25. Rosenfeld, M., S. Casey, M. Pepe, and B.W. Ramsey, *Nutritional effects of long-term gastrostomy feedings in children with cystic fibrosis*. Journal of the American Dietetic Association, 1999. **99**(2): 191-4.
26. Anthony, H., S. Paxton, A. Catto-Smith, and P. Phelan, *Physiological and psychosocial contributors to malnutrition in children with cystic fibrosis: review*. Clinical Nutrition, 1999. **18**(6): 327-35.
27. Anthony, H., A. Catto-Smith, P. Phelan, and S. Paxton, *Current approaches to the nutritional management of cystic fibrosis in Australia*. Journal of Paediatrics & Child Health, 1998. **34**(2): 170-4.
28. Volders, E., *Survey of Nutrition Practice in Australian CF centres. Report for the CF Interest Group of the Dietitians Association of Australia*. 2004.
29. Stapleton, D., H. Anthony, C. Collins, E. Powell, S. King, and C. Mews, *Clinical practice guidelines: Implementing the Australian pancreatic enzyme replacement therapy guidelines for cystic fibrosis*. Australian Journal of Nutrition and Dietetics, 1999. **56**(2): 91-96.
30. Anthony, H., C.E. Collins, G. Davidson, et al., *Pancreatic enzyme replacement therapy in cystic fibrosis: Australian guidelines*. Journal of Paediatrics and Child Health, 1999. **35**(2): 125-9.
31. Collins, C.E. *Review of the Australian Pancreatic Enzyme Replacement Therapy Guidelines in CF. in 4th Australian & New Zealand Cystic Fibrosis Conference*. 2001. Brisbane.
32. UK Cystic Fibrosis Trust, *Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK*. 2001, Cystic Fibrosis Trust: Bromley, Kent, UK.
33. National Health and Medical Research Council, *How to use the evidence: assessment and application of scientific evidence*. 2000, Canberra: Australian Government Publishing Service.
34. Stapleton, D., L. Tunnecliffe, D. McGuiness, J. Sherriff, and P. Sly, *Development of a nutrition and behaviour intervention program: Go and Grow with CF*. Australian Journal of Nutrition and Dietetics, 1998. **55**(3): 130-7.
35. Cystic Fibrosis Foundation, *Patient registry 2004 annual data report*. 2005, Cystic Fibrosis Foundation: Bethesda, Maryland.
36. Massie, J. and B. Clements, *Diagnosis of cystic fibrosis after newborn screening: the Australasian experience--twenty years and five million babies later: a consensus statement from the Australasian Paediatric Respiratory Group*. Pediatric Pulmonology, 2005. **39**(5): 440-6.
37. Jackson, R. and P.B. Pencharz, *Cystic fibrosis*. Best Practice and Research Clinical Gastroenterology, 2003. **17**(2): 213-235.
38. Orenstein, D.M., G.B. Winnie, and H. Altman, *Cystic fibrosis: a 2002 update*. Journal of Pediatrics, 2002. **140**(2): 156-64.
39. Kerem, E., S. Conway, S. Elborn, and H. Heijerman, *Standards of care for patients with cystic fibrosis: a European consensus*. Journal of Cystic Fibrosis, 2005. **4**(1): 7-26.
40. Conway, S.P., A.M. Morton, B. Oldroyd, et al., *Osteoporosis and osteopenia in adults and adolescents with cystic fibrosis: prevalence and associated factors*. Thorax, 2000. **55**(9): 798-804.
41. Haworth, C.S., P.L. Selby, A.K. Webb, et al., *Low bone mineral density in adults with cystic fibrosis*. Thorax, 1999. **54**: 964-967.
42. King, S.J., D.J. Topliss, T.C. Kotsimbos, et al., *Reduced bone density in cystic fibrosis: deltaF508 mutation is an independent risk factor*. European Respiratory Journal, 2005. **25**(1): 54-61.
43. Laursen, E.M., C. Molgaard, K.F. Michaelsen, C. Koch, and J. Muller, *Bone mineral status in 134 patients with cystic fibrosis*. Archives of Disease in Childhood, 1999. **81**: 235-240.
44. Ionescu, A.A., L.S. Nixon, W.D. Evans, et al., *Bone density, body composition, and inflammatory status in cystic fibrosis*. American Journal of Respiratory and Critical Care Medicine, 2000. **162**(3 Pt 1): 789-94.
45. Buntain, H.M., R.M. Greer, P.J. Schluter, et al., *Bone mineral density in Australian children, adolescents and adults with cystic fibrosis: a controlled cross-sectional study*. Thorax, 2004. **59**: 149-155.
46. Farrell, P.M., M.R. Kosorok, M.J. Rock, et al., *Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic Fibrosis Neonatal Screening Study Group.[see comment]*. Pediatrics, 2001. **107**(1): 1-13.
47. Farrell, P.M., M.R. Kosorok, A. Laxova, et al., *Nutritional benefits of neonatal screening for cystic fibrosis. Wisconsin Cystic Fibrosis Neonatal Screening Study Group*. New England Journal of Medicine, 1997. **337**: 963-9.
48. Greer, R., R. Shepherd, G. Cleghorn, F.G. Bowling, and T. Holt, *Evaluation of growth and changes in body composition following neonatal diagnosis of cystic fibrosis*. Journal of Pediatric Gastroenterology and Nutrition, 1991. **13**(1): 52-8.

49. Bines, J.E., H.D. Truby, D.S. Armstrong, P.D. Phelan, and K. Grimwood, *Energy metabolism in infants with cystic fibrosis*. *Journal of Pediatrics*, 2002. **140**(5): 527-33.
50. Kosciak, R.L., P.M. Farrell, M.R. Kosorok, et al., *Cognitive function of children with cystic fibrosis: deleterious effect of early malnutrition*. *Pediatrics*, 2004. **113**(6): 1549-58.
51. Lai, H., M.R. Kosorok, S.A. Sondel, et al., *Growth status in children with cystic fibrosis based on the National Cystic Fibrosis Patient Registry data: evaluation of various criteria used to identify malnutrition*. *Journal of Pediatrics*, 1998. **132**(3): 478-485.
52. Zemel, B.S., D.A. Kawchak, A. Cnaan, H. Zhao, T.F. Scanlin, and V.A. Stallings, *Prospective evaluation of resting energy expenditure, nutritional status, pulmonary function, and genotype in children with cystic fibrosis*. *Pediatric Research*, 1996. **40**(4): 578-86.
53. Thomson, M.A., P. Quirk, C.E. Swanson, et al., *Nutritional growth retardation is associated with defective lung growth in cystic fibrosis: a preventable determinant of progressive pulmonary dysfunction*. *Nutrition*, 1995. **11**(4): 350-354.
54. Stettler, N., D.A. Kawchak, L.L. Boyle, et al., *Prospective evaluation of growth, nutritional status, and body composition in children with cystic fibrosis*. *American Journal of Clinical Nutrition*, 2000. **72**(2): 407-13.
55. Bell, S.C., A.R. Bowerman, C.A. Davies, I.A. Campbell, D.J. Shale, and J.S. Elborn, *Nutrition in adults with cystic fibrosis*. *Clinical Nutrition*, 1998. **17**(5): 211-5.
56. Cystic Fibrosis Foundation, *Patient registry 2001 annual report*. 2002, Cystic Fibrosis Foundation: Bethesda, Maryland.
57. Bell, S.C. and R.W. Shepherd, *Optimising nutrition in cystic fibrosis*. *Journal of Cystic Fibrosis*, 2002. **1**: 47-50.
58. Wilson, D.C. and P.B. Pencharz, *Nutrition and cystic fibrosis*. *Nutrition*, 1998. **14**: 792-795.
59. Borowitz, D., *The interrelationship of nutrition and pulmonary function in patients with cystic fibrosis*. *Current Opinion in Pulmonary Medicine*, 1996. **2**: 457-461.
60. Wootton, S.A., J.L. Murphy, S.A. Bond, J.E. Ellis, and A.A. Jackson, *Energy balance and growth in cystic fibrosis*. *Journal of the Royal Society of Medicine*, 1991. **84**(18): 22-27.
61. Bell, S.C., M.J. Saunders, J.S. Elborn, and D.J. Shale, *Resting energy expenditure and oxygen cost of breathing in patients with cystic fibrosis*. *Thorax*, 1996. **51**(2): 126-31.
62. Shepherd, R.W., R.M. Greer, S.A. McNaughton, M. Wotton, and G.J. Cleghorn, *Energy expenditure and the body cell mass in cystic fibrosis*. *Nutrition*, 2001. **17**: 22-25.
63. Selvadurai, H.C., J. Allen, T. Sachinwalla, J. Macauley, C.J. Blimkie, and P.P. Van Asperen, *Muscle function and resting energy expenditure in female athletes with cystic fibrosis*. *American Journal of Respiratory and Critical Care Medicine*, 2003. **168**(12): 1476-80.
64. Richards, M.L., P.S. Davies, and S.C. Bell, *Energy cost of physical activity in cystic fibrosis*. *European Journal of Clinical Nutrition*, 2001. **55**(8): 690-7.
65. Dorlochter, L., O. Roksund, V. Helgheim, K. Rosendahl, and G. Fluge, *Resting energy expenditure and lung disease in cystic fibrosis*. *Journal of Cystic Fibrosis*, 2002. **1**: 131-136.
66. Allen, J.R., J.C. McCauley, A.M. Selby, et al., *Differences in resting energy expenditure between male and female children with cystic fibrosis*. *Journal of Pediatrics*, 2003. **142**(1): 15-9.
67. Pencharz, P.B. and R. Jackson, *There is no evidence of a primary defect in energy metabolism in subjects with cystic fibrosis*. *Journal of Pediatrics*, 2002. **140**(5): 498-9.
68. McCloskey, M., A.O.B. Redmond, C. McCabe, S. Pyper, K.R. Westerterp, and S.J. Elborn, *Energy balance in cystic fibrosis when stable and during a respiratory exacerbation*. *Clinical Nutrition*, 2004. **23**(6): 1405-1412.
69. McCloskey, M., A.O. Redmond, S. Pyper, C. McCabe, K.R. Westerterp, and J.S. Elborn, *Total energy expenditure in stable patients with cystic fibrosis*. *Clinical Nutrition*, 2001. **20**(3): 235-41.
70. Spicher, V., M. Roulet, and Y. Schutz, *Assessment of total energy expenditure in free-living patients with cystic fibrosis*. *Journal of Pediatrics*, 1991. **118**: 865-872.
71. Kalivianakis, M. and H.J. Verkade, *The mechanisms of fat malabsorption in cystic fibrosis patients*. *Nutrition*, 1999. **15**(2): 167-9.
72. Murphy, J.L. and S.A. Wootton, *Nutritional management in cystic fibrosis- an alternative perspective in gastrointestinal function*. *Disability and Rehabilitation*, 1998. **20**: 226-234.
73. Stead, R.J., I. Skypala, M.E. Hodson, and J.C. Batten, *Enteric coated microspheres of pancreatin in the treatment of cystic fibrosis: comparison with a standard enteric coated preparation*. *Thorax*, 1987. **42**(7): 533-37.
74. Kalnins, D., P.R. Durie, and L. Ellis, *Pancreatic enzymes-evaluation of current practice in a large CF clinic*. *Pediatric Pulmonology*, 1995. **20**: 266.

75. Kalivianakis, M., D. Minich, C. Bijleveld, et al., *Fat malabsorption in cystic fibrosis patients receiving enzyme replacement therapy is due to impaired intestinal uptake of long-chain fatty acids*. American Journal of Clinical Nutrition, 1999. **69**: 127-134.
76. Stapleton, D., C. Mews, M. Bulsara, J. Sherriff, and P. Sly, *Pancreatic enzyme replacement therapy: adherence to guidelines*. Nutrition and Dietetics, 2002. **59**: 260-264.
77. Durie, P., D. Kalnins, and L. Ellis, *Uses and abuses of enzyme therapy in cystic fibrosis*. Journal of the Royal Society of Medicine, 1998. **91**:(Suppl): 2-13.
78. Collins, C.E., E. O'Loughlin, and R.L. Henry, *Fat gram target to achieve high energy intake in cystic fibrosis*. Journal of Paediatrics and Child Health, 1997. **31**: 142-147.
79. Anthony, H., J. Bines, P. Phelan, and S. Paxton, *Relation between dietary intake and nutritional status in cystic fibrosis*. Archives of Disease in Childhood, 1998. **78**: 443-7.
80. Murphy, J.L., S.A. Wootton, S.A. Bond, and A.A. Jackson, *Energy content of stools in normal healthy controls and patients with cystic fibrosis*. Archives of Disease in Childhood, 1991. **66**: 495-500.
81. Forstner, G. and P.R. Durie, *Cystic Fibrosis*, in *Pediatric Gastrointestinal Disease: Pathology, Diagnosis & Management*, W.A. Walker, P.R. Durie, J.R. Hamilton, J.A. Walker-Smith, and J.B. Watkins, Editors. 1991, BC Decker Inc: Ontario. p. 1191.
82. Powers, S.W. and S.R. Patton, *A comparison of nutrient intake between infants and toddlers with and without cystic fibrosis*. Journal of the American Dietetic Association, 2003. **103**(12): 1620-5.
83. White, H., A.M. Morton, D.G. Peckham, and S.P. Conway, *Dietary intakes in adults with cystic fibrosis - do they achieve guidelines?* Journal of Cystic Fibrosis, 2004. **3**: 1-7.
84. Ellis, J.A., S.A. Bond, and S.A. Wootton, *Energy and protein intakes of patients with cystic fibrosis*. Journal of Human Nutrition and Dietetics, 1992. **5**: 333-342.
85. Dodge, J.A., *Nutritional requirements in cystic fibrosis: a review*. Journal of Pediatric Gastroenterology and Nutrition, 1988. **7**(Suppl. 1): S8-S11.
86. Hubbard, V.S. *Nutrient requirements of patients with cystic fibrosis*. in *the 8th International Cystic Fibrosis Congress Proceedings*. 1980. Toronto: Canadian Cystic Fibrosis Foundation.
87. Bentur, L., D. Kalnins, H. Levison, M. Corey, and P.R. Durie, *Dietary intakes of young children with cystic fibrosis: is there a difference?* Journal of Pediatric Gastroenterology and Nutrition, 1996. **22**(3): 254-258.
88. Kawchak, D.A., H. Zhao, T.F. Scanlin, J.L. Tomezsko, A. Cnaan, and V.A. Stallings, *Longitudinal, prospective analysis of dietary intake in children with cystic fibrosis*. Journal of Pediatrics, 1996. **129**: 119-129.
89. Stark, L.J., E. Jelalian, M.M. Mulvihill, et al., *Eating in preschool children with cystic fibrosis and healthy peers: behavioural analysis*. Pediatrics, 1995. **95**(2): 210-215.
90. Tomezsko, J.L., V.A. Stallings, and T.F. Scanlin, *Dietary intake of healthy children with cystic fibrosis compared with normal control children*. Pediatrics, 1992. **90**(4): 547-553.
91. Walkowiak, J. and J. Przyslawski, *Five-year prospective analysis of dietary intake and clinical status in malnourished cystic fibrosis patients*. Journal of Human Nutrition and Dietetics, 2003. **16**: 225-231.
92. Powers, S.W., S.R. Patton, K.C. Byars, et al., *Caloric intake and eating behavior in infants and toddlers with cystic fibrosis*. Pediatrics, 2002. **109**(5): E75-5.
93. Gibson, R.S., *Principles of nutritional assessment*. 1990, New York: Oxford University Press.
94. Vic, P., S. Ategbo, F. Gottrand, et al., *Nutritional impact of antipseudomonas intravenous antibiotic courses in cystic fibrosis*. Archives of Disease in Childhood, 1997. **76**(5): 437-40.
95. Wood, L.G., P.G. Gibson, and M.L. Garg, *Circulating markers to assess nutritional therapy in cystic fibrosis*. Clinica Chimica Acta, 2005. **353**(1-2): 13-29.
96. Matson, A.G., F. Walker, K.M. Matson, and S.C. Bell, *Prevalence of cystic fibrosis related diabetes in an adult Australian cystic fibrosis unit*. Pediatric Pulmonology. Supplement, 2002. **24**: 336.
97. Nixon, L.S., B. Yung, S.C. Bell, J.S. Elborn, and D.J. Shale, *Circulating immunoreactive interleukin-6 in cystic fibrosis*. American Journal of Respiratory and Critical Care Medicine, 1998. **157**: 1764-1769.
98. Shils, M.E., J.A. Olson, M. Shike, and A.C. Ross, *Modern nutrition in health and disease*. 1999, Baltimore, Maryland: Williams & Wilkins.
99. Ionescu, A.A., L.S. Nixon, S. Luzio, et al., *Pulmonary function, body composition, and protein catabolism in adults with cystic fibrosis*. American Journal of Respiratory and Critical Care Medicine, 2002. **165**(4): 495-500.
100. Jelalian, E., L.J. Stark, L. Reynolds, and R. Seifer, *Nutrition intervention for weight gain in cystic fibrosis: a meta analysis*. Journal of Pediatrics, 1998. **132**(3): 486-492.

101. MacDonald, A., *Nutritional management of cystic fibrosis*. Archives of Disease in Childhood, 1996. **74**: 81-87.
102. Gudas, L.J., G.P. Koocher, and D. Wypij, *Perceptions of medical compliance in children and adolescents with cystic fibrosis*. Developmental and Behavioural Pediatrics, 1991. **12**(4): 236-242.
103. Henley, L.D. and I. Hill, *Global and specific disease-related information needs of cystic fibrosis patients and their families*. Pediatrics, 1990. **85**: 1008-1014.
104. McCabe, H., *Cystic fibrosis- what nutritional knowledge do patients have?* Journal of Human Nutrition and Dietetics, 1996. **9**: 479-486.
105. Stapleton, D.R., L.C. Gurrin, S.R. Zubrick, S.R. Silburn, J.L. Sherriff, and P.D. Sly, *What do children with cystic fibrosis and their parents know about nutrition and pancreatic enzymes?* Journal of the American Dietetic Association, 2000. **100**(12): 1494-1500.
106. Crist, W., P. McDonnell, M. Beck, C.T. Gillespie, P. Barrett, and J. Mathews, *Behaviour at mealtimes and the young child with cystic fibrosis*. Journal of Developmental and Behavioural Pediatrics, 1994. **15**(3): 157-161.
107. Sanders, M.R., F.M. Gravestock, K. Wanstall, and M. Dunne, *The relationship between children's treatment-related behaviour problems, age and clinical status in cystic fibrosis*. Journal of Paediatrics and Child Health, 1991. **27**: 290-294.
108. Stark, L.J., E. Jelalian, S.W. Powers, et al., *Parent and child mealtime behavior in families of children with cystic fibrosis*. Journal of Pediatrics, 2000. **136**(2): 195-200.
109. Stark, L.J., S.W. Powers, E. Jelalian, R.N. Rape, and D.L. Miller, *Modifying problematic mealtime interactions of children with cystic fibrosis and their parents via behavioural parent training*. Journal of Pediatric Psychology, 1994. **19**(6): 751-768.
110. Stark, L., M. Mulvihill, E. Powers, et al., *Behavioural intervention to improve calorie intake of children with cystic fibrosis: treatment versus wait list control*. Journal of Pediatric Gastroenterology and Nutrition, 1996. **22**(3): 240-253.
111. Stark, L.J., J. Owens-Stively, A. Spirito, A. Lewis, and D. Guevremont, *Group behavioural treatment of retentive encopresis*. Journal of Pediatric Psychology, 1990. **15**(5): 659-671.
112. Singer, L. *Behavioural approaches to feeding problems: intervention with infants*. in 1994 Cystic Fibrosis Conference. 1994.
113. Duff, A.J., S.P. Wolfe, C. Dickson, S.P. Conway, and K.G. Brownlee, *Feeding behavior problems in children with cystic fibrosis in the UK: prevalence and comparison with healthy controls*. Journal of Pediatric Gastroenterology and Nutrition, 2003. **36**(4): 443-7.
114. Truby, H. and A.S. Paxton, *Body image and dieting behavior in cystic fibrosis*. Pediatrics, 2001. **107**(6): E92.
115. Walters, S., *Sex differences in weight perception and nutritional behaviour in adults with cystic fibrosis*. Journal of Human Nutrition and Dietetics, 2001. **14**(2): 83-91.
116. Shearer, J.E. and M. Bryon, *The nature and prevalence of eating disorders and eating disturbance in adolescents with cystic fibrosis*. Journal of the Royal Society of Medicine, 2004. **97**(Suppl 4): 36-42.
117. Raymond, N.C., P.N. Chang, S.J. Crow, et al., *Eating disorders in patients with cystic fibrosis*. Journal of Adolescence, 2000. **23**: 359-63.
118. Abbott, J., S. Conway, C. Etherington, et al., *Perceived body image and eating behavior in young adults with cystic fibrosis and their healthy peers*. Journal of Behavioral Medicine, 2000. **23**: 501-17.
119. Liptak, G.S., *Enhancing patient compliance in pediatrics*. Pediatrics in Review, 1996. **17**(4): 128-133.
120. Fielding, D. and A. Duff, *Compliance with treatment protocols: interventions for children with chronic illness*. Archives of Disease in Childhood, 1999. **80**: 196-200.
121. Victorian Clinical Standards Advisory Group, *Cystic fibrosis care quality of care guidelines*. 1999: Melbourne.
122. British Paediatric Association, *Cystic fibrosis in the United Kingdom 1977-85; an improving picture*. BMJ, 1988. **297**: 1599-1602.
123. Royal College of Physicians, *Cystic fibrosis in adults: recommendations for care of patients in the United Kingdom*. 1990, RCP: London.
124. Reilly, J.J., C.A. Edwards, and L.T. Weaver, *Malnutrition in children with cystic fibrosis: the energy-balance equation*. Journal of Pediatric Gastroenterology and Nutrition, 1997. **25**: 127-136.
125. Stapleton, D., D. Kerr, L. Gurrin, J. Sherriff, and P. Sly, *Height and weight fail to detect early signs of malnutrition in children with cystic fibrosis*. Journal of Pediatric Gastroenterology and Nutrition, 2001. **33**(3): 319-25.
126. National Health and Medical Research Council, *Food for Health: Dietary guidelines for children and adolescents in Australia*. 2003, Canberra: Australian Government Publishing Service.

127. Gibson, R.S., *Nutritional assessment a laboratory manual*. 1993, New York ? check from Maggie Aitken: Oxford University Press.
128. Zhang, Z. and H.J. Lai, *Comparison of the use of body mass index percentiles and percentage of ideal body weight to screen for malnutrition in children with cystic fibrosis*. American Journal of Clinical Nutrition, 2004. **80**(4): 982-91.
129. Schutz, Y., U.U. Kyle, and C. Pichard, *Fat-free mass index and fat mass index percentiles in Caucasians aged 18-98 y*. International Journal of Obesity and Related Metabolic Disorders, 2002. **26**(7): 953-60.
130. Wells, J.C., *A critique of the expression of paediatric body composition data*. Archives of Disease in Childhood, 2001. **85**(1): 67-72.
131. Sood, M., J.E. Adams, and M.Z. Mughal, *Lean body mass in children with cystic fibrosis*. Archives of Disease in Childhood, 2003. **88**(9): 836.
132. Haslam, R.H.M., D.J. Borovnicar, D.B. Stroud, B.J.G. Strauss, and J.E. Bines, *Correlates of prepubertal bone mineral density in cystic fibrosis*. Archives of Disease in Childhood, 2001. **85**: 166-171.
133. Tomezsko, J.L., T.F. Scanlin, and V.A. Stallings, *Body composition of children with cystic fibrosis with mild clinical manifestations compared with normal children*. American Journal of Clinical Nutrition, 1994. **59**(1): 123-8.
134. Bolton, C.E., A.A. Ionescu, W.D. Evans, R.J. Pettit, and D.J. Shale, *Altered tissue distribution in adults with cystic fibrosis*. Thorax, 2003. **58**(10): 885-9.
135. Johnston, J.L., M.S. Leong, E.G. Checkland, P.C. Zuberbuhler, P.R. Conger, and H.A. Quinney, *Body fat assessed from body density and estimated from skinfold thickness in normal children and children with cystic fibrosis*. American Journal of Clinical Nutrition, 1988. **48**: 1362-1366.
136. Ahmed, M.L., K.K. Ong, A.H. Thomson, and D.B. Dunger, *Reduced gains in fat and fat-free mass, and elevated leptin levels in children and adolescents with cystic fibrosis*. Acta Paediatrica, 2004. **93**: 1185-91.
137. Peterson, M.L., D.R. Jacobs, Jr., and C.E. Milla, *Longitudinal changes in growth parameters are correlated with changes in pulmonary function in children with cystic fibrosis*. Pediatrics, 2003. **112**(3 (pt 1)): 588-92.
138. Shepherd, R.W., T.L. Holt, R. Greer, G.J. Cleghorn, and B.J. Thomas, *Total body potassium in cystic fibrosis*. Journal of Pediatric Gastroenterology and Nutrition, 1989. **9**(2): 200-5.
139. Borovnicar, D.J., D.B. Stroud, J.E. Bines, R.H. Haslam, and B.J. Strauss, *Comparison of total body chlorine, potassium, and water measurements in children with cystic fibrosis*. American Journal of Clinical Nutrition, 2000. **71**(1): 36-43.
140. Grey, A.B., R.W. Ames, R.D. Matthews, and I.R. Reid, *Bone mineral density and body composition in adult patients with cystic fibrosis*. Thorax, 1993. **48**: 589-593.
141. Rochat, T., D.O. Slosman, C. Pichard, and D.C. Belli, *Body composition analysis by dual-energy x-ray absorptiometry in adults with cystic fibrosis*. Chest, 1994. **106**(3): 800-5.
142. McNaughton, S.A., R.W. Shepherd, R.G. Greer, G.J. Cleghorn, and B.J. Thomas, *Nutritional status of children with cystic fibrosis measured by total body potassium as a marker of body cell mass: lack of sensitivity of anthropometric measures*. Journal of Pediatrics, 2000. **136**(2): 188-94.
143. King, S.J., J.W. Wilson, T. Kotsimbos, B.J. Strauss, and I.B. Nyulasi, *Body mass index (BMI) as an indicator of malnutrition fails to detect fat-free mass depletion in adults with cystic fibrosis*. Pediatric Pulmonology, 2004. **Supplement 27**: 330.
144. Mueller, W.H. and H.J. Kaplowitz, *The precision of anthropometric assessment of body fat distribution in children*. Annals of Human Biology, 1994. **21**(3): 267-274.
145. Norton, K., N. Whittingham, L. Carter, D. Kerr, C. Gore, and M. Marfell-Jones, *Measurement Techniques in Anthropometry*, in *Anthropometrica: a textbook of body measurement for sports and health courses*, T. Olds and K. Norton, Editors. 1996, University of New South Wales Press: Sydney. p. 53.
146. Durnin, J.V.G.A. and J. Womersley, *Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16-72 years*. British Journal of Nutrition, 1974. **32**: 77-97.
147. Lands, L.C., C. Gordon, O. Bar-Or, et al., *Comparison of three techniques for body composition analysis in cystic fibrosis*. Journal of Applied Physiology, 1993. **75**(1): 162-6.
148. de Meer, K., V.A. Gulmans, K.R. Westerterp, R.H. Houwen, and R. Berger, *Skinfold measurements in children with cystic fibrosis: monitoring fat-free mass and exercise effects*. European Journal of Pediatrics, 1999. **158**(10): 800-6.

149. King, S.J., J.W. Wilson, T.C. Kotsimbos, M. Bailey, and I.B. Nyulasi, *Body composition assessment in adults with cystic fibrosis: comparison of Dual-Energy X-ray absorptiometry with skinfolds and Bioelectrical Impedance Analysis*. Nutrition, 2005. **21**: 1087-1094.
150. Groeneweg, M., S. Tan, A.M. Boot, J.C. de Jongste, J. Bouquet, and M. Sinaasappel, *Assessment of nutritional status in children with cystic fibrosis: conventional anthropometry and bioelectrical impedance analysis. A cross-sectional study in Dutch patients*. Journal of Cystic Fibrosis, 2002. **1**: 276-280.
151. Rockett, H.R.H. and G.A. Colditz, *Assessing diets of children and adolescents*. American Journal of Clinical Nutrition, 1997. **65(Suppl)**: 1116S-1122S.
152. Daniels, L.A. and G.P. Davidson, *Current issues in the nutritional management of children with cystic fibrosis*. Australian Paediatric Journal, 1989. **25**: 261-266.
153. Philips, J., J. Bajramovic, and S. Bell. *A study of the use of complementary and alternative medicines in adults with cystic fibrosis*. in *Fourth Australian and New Zealand Cystic Fibrosis Conference*. 2001.
154. Lancellotti, L., C. D'Orazio, G. Mastella, G. Mazzi, and U. Lippi, *Deficiency of vitamins E and A in cystic fibrosis is independent of pancreatic function and current enzyme and vitamin supplementation*. European Journal of Pediatrics, 1996. **155**: 281-285.
155. Greer, R.M., H.M. Buntain, P.J. Lewindon, et al., *Vitamin A levels in patients with CF are influenced by the inflammatory response*. Journal of Cystic Fibrosis, 2004. **3(3)**: 143-149.
156. Brennan, A.L., D.M. Geddes, K.M. Gyi, and E.H. Baker, *Clinical importance of cystic fibrosis-related diabetes*. Journal of Cystic Fibrosis, 2004. **3**: 209-222.
157. UK Cystic Fibrosis Trust Diabetes Working Group, *Management of cystic fibrosis related diabetes mellitus*. 2004, Cystic Fibrosis Trust: Bromley, Kent, UK.
158. Moran, A., D. Hardin, D. Rodman, et al., *Diagnosis, screening and management of cystic fibrosis related diabetes mellitus: a consensus conference report*. Diabetes Research & Clinical Practice, 1999. **45(1)**: 61-73.
159. Dobson, L., C.D. Sheldon, and A.T. Hattersley, *Conventional measures underestimate glycaemia in cystic fibrosis patients*. Diabetic Medicine, 2004. **21(7)**: 691-6.
160. Keevil, B., D. Rowlands, I. Burton, and A.K. Webb, *Assessment of iron status in cystic fibrosis patients*. Annals of Clinical Biochemistry, 2000. **37(Pt 5)**: 662-665.
161. Solomons, N.W. and R.M. Russell, *The interaction of vitamin A and zinc: implications for human nutrition*. American Journal of Clinical Nutrition, 1980. **33**: 2031-2040.
162. Ramsey, B., P. Farrell, and P. Pencharz, *Nutritional assessment and management in cystic fibrosis: a consensus report*. American Journal of Clinical Nutrition, 1992. **55**: 108-116.
163. Littlewood, J.M. and A. MacDonald, *Rationale of modern dietary recommendations in cystic fibrosis*. Journal of the Royal Society of Medicine, 1987. **80**: 16-23.
164. Murphy, M.D., C.S. Ireton-Jones, B.C. Hilman, M.A. Gorman, and G.U. Liepa, *Resting energy expenditures measured by indirect calorimetry are higher in preadolescent children with cystic fibrosis than expenditures calculated from prediction equations*. Journal of the American Dietetic Association, 1995. **95(1)**: 30-3.
165. Reilly, J.J., T.J. Evans, J. Wilkinson, and J.Y. Paton, *Adequacy of clinical formulae for estimation of energy requirements in children with cystic fibrosis*. Archives of Disease in Childhood, 1999. **81(2)**: 120-4.
166. Marin, V.B., S. Velandia, B. Hunter, et al., *Energy expenditure, nutrition status, and body composition in children with cystic fibrosis*. Nutrition, 2004. **20(2)**: 181-6.
167. Bell, L., P. Durie, and G. Forstner, *What do children with cystic fibrosis eat?* Journal of Pediatric Gastroenterology and Nutrition, 1984. **3(Suppl)**: S137-46.
168. Shepherd, R.W., T.L. Holt, B.J. Thomas, L.C. Ward, A. Isles, and P.J. Francis, *Malnutrition in cystic fibrosis: the nature of the nutritional deficit and optimal management*. Nutrition Abstracts and Reviews in Clinical Nutrition, 1984. **54(12)**: 1009-1020.
169. Slesinski, M.J., M.F. Gloninger, J.P. Costantino, and D.M. Orenstein, *Lipid levels in adults with cystic fibrosis*. Journal of the American Dietetic Association., 1994. **94(4)**: 402-8.
170. National Health and Medical Research Council, *Recommended dietary intakes for use in Australia*. 1991, Canberra: Australian Government Publishing Service.
171. Kien, C.L., W.B. Zipf, C.A. Horswill, S.C. Denne, K.S. McCoy, and T.M. O'Dorisio, *Effects of feeding on protein turnover in healthy children and in children with cystic fibrosis*. American Journal of Clinical Nutrition, 1996. **64(4)**: 608-14.
172. Erdman, S.H., *Nutritional imperatives in cystic fibrosis therapy*. Pediatric Annals, 1999. **28(2)**: 129-36.

173. Gavin, J., J. Ellis, A.L. Dewar, C.J. Rolles, and G.J. Connett, *Dietary fibre and the occurrence of gut symptoms in cystic fibrosis*. Archives of Disease in Childhood, 1997. **76**: 35-37.
174. Proesmans, M. and K. De Boeck, *Evaluation of dietary fiber intake in Belgian children with cystic fibrosis: is there a link with gastrointestinal complaints?* Journal of Pediatric Gastroenterology and Nutrition, 2002. **35**(5): 610-4.
175. Feranchak, A.P., M.K. Sontag, J.S. Wagener, K.B. Hammond, F.J. Accurso, and R.J. Sokol, *Prospective, long-term study of fat-soluble vitamin status in children with cystic fibrosis identified by newborn screen*. Journal of Pediatrics, 1999. **135**(5): 601-10.
176. Sokol, R.J., M.C. Reardon, F.J. Accurso, et al., *Fat-soluble-vitamin status during the first year of life in infants with cystic fibrosis identified by screening of newborns*. American Journal of Clinical Nutrition, 1989. **50**(5): 1064-71.
177. Rayner, R.J., J.C. Tyrrell, E.J. Hiller, et al., *Night blindness and conjunctival xerosis caused by vitamin A deficiency in patients with cystic fibrosis*. Archives of Disease in Childhood, 1989. **64**(8): 1151-6.
178. Gavin, J., J. Murphy, G. Connett, M. Carroll, A. Cawood, and S. Wootton, *Vitamin A supplements in children with CF - are we giving too much?* Journal of Cystic Fibrosis, 2003. **2**: S88.
179. Cawood, A.L., J.L. Murphy, M.P. Carroll, et al., *Altered availability and mobilisation of vitamin A in CF*. Journal of Cystic Fibrosis, 2003. **2**: S87.
180. Cawood, A.L., J.L. Murphy, M.P. Carroll, et al., *Circulating plasma retinol concentrations and infection in patients with cystic fibrosis*. Journal of Cystic Fibrosis, 2002. **1**: S145.
181. Jaffe, A., R. Buchdahl, A. Bush, and I.M. Balfour-Lynn, *Are annual blood tests in preschool cystic fibrosis patients worthwhile?* Archives of Disease in Childhood, 2002. **87**(6): 518-20.
182. Huet, F., D. Semama, C. Maingueneau, A. Charavel, and J.L. Nivelon, *Vitamin A deficiency and nocturnal vision in teenagers with cystic fibrosis*. European Journal of Pediatrics, 1997. **156**(12): 949-51.
183. Eid, N.S., L.R. Shoemaker, and T.D. Samiec, *Vitamin A in cystic fibrosis: a case report and review of the literature*. Journal of Pediatrics, 1990. **10**: 265-269.
184. Duggan, C., A.A. Colin, A. Agil, L. Higgins, and N. Rifai, *Vitamin A status in acute exacerbations of cystic fibrosis*. American Journal of Clinical Nutrition, 1996. **64**(4): 635-9.
185. MacDonald, A., C. Holden, and G. Harris, *Nutritional strategies in cystic fibrosis: current issues*. Journal of the Royal Society of Medicine, 1991. **84**(18): 28-35.
186. Chavasse, R.J., J. Francis, I. Balfour-Lynn, M. Rosenthal, and A. Bush, *Serum vitamin D levels in children with cystic fibrosis*. Pediatric Pulmonology, 2004. **38**(2): 119-22.
187. Henderson, R.C. and C.D. Madsen, *Bone density in children and adults with cystic fibrosis*. Journal of Pediatrics, 1996. **128**: 28-34.
188. Vieth, R., *Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety.[see comment]*. American Journal of Clinical Nutrition, 1999. **69**(5): 842-56.
189. Malabanan, A., I.E. Veronikis, and M.F. Holick, *Redefining vitamin D insufficiency*. Lancet, 1998. **351**(9105): 805-6.
190. Holick, M.F., *Too little vitamin D in premenopausal women: why should we care?* American Journal of Clinical Nutrition, 2002. **76**(1): 3-4.
191. Chia, A.L., S. Shumack, and P. Foley, *Vitamin D and adult bone health in Australia and New Zealand: a position statement*. Medical Journal of Australia, 2005. **183**(1): 52-3; author reply 53-4.
192. Aris, R.M., P.A. Merkel, L.K. Bachrach, et al., *Consensus statement: guide to bone health and disease in cystic fibrosis*. Journal of Clinical Endocrinology and Metabolism, 2005. **90**(3): 1888-96.
193. Thomas, M.K., D.M. Lloyd-Jones, R.I. Thadhani, et al., *Hypovitaminosis D in medical inpatients*. New England Journal of Medicine, 1998. **338**: 777-783.
194. Cooper, L., P.B. Clifton-Bligh, M.L. Nery, et al., *Vitamin D supplementation and bone mineral density in early postmenopausal women*. American Journal of Clinical Nutrition, 2003. **77**(5): 1324-9.
195. Wilfond, B.S., P.M. Farrell, A. Laxova, and E. Mischler, *Severe hemolytic anemia associated with vitamin E deficiency in infants with cystic fibrosis. Implications for neonatal screening*. Clinical Pediatrics, 1994. **33**(1): 2-7.
196. Winklhofer-Roob, B.M., M.A. van't Hof, and D.H. Shmerling, *Long-term oral vitamin E supplementation in cystic fibrosis patients: RRR-alpha-tocopherol compared with all-rac-alpha-tocopheryl acetate preparations*. American Journal of Clinical Nutrition, 1996. **63**(5): 722-728.
197. Hathcock, J.N., A. Azzi, J. Blumberg, et al., *Vitamins E and C are safe across a broad range of intakes*. American Journal of Clinical Nutrition, 2005. **81**(4): 736-45.

198. Durie, P.R., *Vitamin K and the management of patients with cystic fibrosis*. CMAJ Canadian Medical Association Journal, 1994. **151**(7): 933-6.
199. Rashid, M., P. Durie, M. Andrew, et al., *Prevalence of vitamin K deficiency in cystic fibrosis*. American Journal of Clinical Nutrition, 1999. **70**(3): 378-82.
200. Wilson, D.C., M. Rashid, P.R. Durie, et al., *Treatment of vitamin K deficiency in cystic fibrosis: Effectiveness of a daily fat-soluble vitamin combination*. Journal of Pediatrics, 2001. **138**(6): 851-5.
201. Conway, S.P., S.P. Wolfe, K.G. Brownlee, et al., *Vitamin K status among children with cystic fibrosis and its relationship to bone mineral density and bone turnover*. Pediatrics, 2005. **115**(5): 1325-31.
202. Beker, L.T., R.A. Ahrens, R.J. Fink, et al., *Effect of vitamin K1 supplementation on vitamin K status in cystic fibrosis patients*. Journal of Pediatric Gastroenterology and Nutrition, 1997. **24**(5): 512-7.
203. McCabe, H.E., J.K. Johnson, and C. O'Brien, *B vitamin deficiency in the paediatric cystic fibrosis population*. Pediatric Pulmonology, 2004. **Supplement 27**: 338-339.
204. Kriemler, S., B. Wilk, W. Schurer, W.M. Wilson, and O. Bar-Or, *Preventing dehydration in children with cystic fibrosis who exercise in the heat*. Medicine and Science in Sports and Exercise, 1999. **31**(6): 774-9.
205. Ozcelik, U., A. Gocmen, N. Kiper, T. Coskun, E. Yilmaz, and M. Ozguc, *Sodium chloride deficiency in cystic fibrosis patients*. European Journal of Pediatrics, 1994. **153**(11): 829-31.
206. Russo, M.A., C. Hogenauer, S.W. Coates, Jr., et al., *Abnormal passive chloride absorption in cystic fibrosis jejunum functionally opposes the classic chloride secretory defect*. Journal of Clinical Investigation, 2003. **112**(1): 118-25.
207. Reid, D.W., N.J. Withers, L. Francis, J.W. Wilson, and T.C. Kotsimbos, *Iron deficiency in cystic fibrosis: relationship to lung disease severity and chronic Pseudomonas aeruginosa infection*. Chest, 2002. **121**(1): 48-54.
208. Pond, M.N., A.M. Morton, and S.P. Conway, *Functional iron deficiency in adults with cystic fibrosis*. Respiratory Medicine, 1996. **90**(7): 409-13.
209. Ehrhardt, P., M.G. Miller, and J.M. Littlewood, *Iron deficiency in cystic fibrosis*. Archives of Disease in Childhood, 1987. **62**(2): 185-7.
210. Ater, J.L., J.J. Herbst, S.A. Landaw, and R.T. O'Brien, *Relative anemia and iron deficiency in cystic fibrosis*. Pediatrics, 1983. **71**(5): 810-4.
211. Schulze, K.J., K.O. O'Brien, E.L. Germain-Lee, D.J. Baer, A. Leonard, and B.J. Rosenstein, *Efficiency of calcium absorption is not compromised in clinically stable prepubertal and pubertal girls with cystic fibrosis*. American Journal of Clinical Nutrition, 2003. **78**(1): 110-6.
212. Aris, R.M., D.A. Ontjes, S.A. Brown, W. Chalermkulrat, I. Neuringer, and G.E. Lester, *Carboxylated osteocalcin levels in cystic fibrosis*. American Journal of Respiratory and Critical Care Medicine, 2003. **168**(9): 1129.
213. Sambrook, P.N. and J.A. Eisman, *Osteoporosis prevention and treatment*. Medical Journal of Australia, 2000. **172**(5): 226-9.
214. O'Neill, S., P. Sambrook, T. Diamond, et al., *Guidelines for the treatment of postmenopausal osteoporosis for general practitioners*. Australian Family Physician, 2002. **31**(10): 1-8.
215. Portal, B.C., M.J. Richard, H.S. Faure, A.J. Hadjian, and A.E. Favier, *Altered antioxidant status and increased lipid peroxidation in children with cystic fibrosis*. American Journal of Clinical Nutrition, 1995. **61**(4): 843-7.
216. Winklhofer-Roob, B.M., S.E. Schlegel-Haueter, G. Khoschorur, M.A. van't Hof, S. Suter, and D.H. Shmerling, *Neutrophil elastase/alpha 1-proteinase inhibitor complex levels decrease in plasma of cystic fibrosis patients during long-term oral beta-carotene supplementation*. Pediatric Research, 1996. **40**(1): 130-4.
217. Shelhamer, J.H., S.J. Levine, T. Wu, D.B. Jacoby, M.A. Kaliner, and S.I. Rennard, *NIH conference. Airway inflammation*. Annals of Internal Medicine, 1995. **123**(4): 288-304.
218. Christophe, A. and E. Robberecht, *Current knowledge on fatty acids in cystic fibrosis*. Prostaglandins Leukotrienes and Essential Fatty Acids, 1996. **55**(3): 129-38.
219. Beckles Willson, N., T.M. Elliott, and M.L. Everard, *Omega-3 fatty acids (from fish oils) for cystic fibrosis*. Cochrane Database of Systematic Reviews, 2002(3): CD002201.
220. Bruzzese, E., V. Raia, G. Gaudiello, et al., *Intestinal inflammation is a frequent feature of cystic fibrosis and is reduced by probiotic administration*. Alimentary Pharmacology and Therapeutics, 2004. **20**(7): 813-9.
221. Guarino, A., *Effects of probiotics in children with cystic fibrosis*. Gastroenterology International, 1998. **11**(Supplement 1): 91.

222. Gluck, U. and J.O. Gebbers, *Ingested probiotics reduce nasal colonization with pathogenic bacteria (Staphylococcus aureus, Streptococcus pneumoniae, and beta-hemolytic streptococci)*. American Journal of Clinical Nutrition, 2003. **77**(2): 517-20.
223. Agostoni, C., I. Axelsson, C. Braegger, et al., *Probiotic Bacteria in Dietetic Products for Infants: A Commentary by the ESPGHAN Committee on Nutrition*. Journal of Pediatric Gastroenterology and Nutrition, 2004. **38**(4): 365-374.
224. Walker, S.A. and D. Gozal, *Pulmonary function correlates in the prediction of long-term weight gain in cystic fibrosis patients with gastrostomy tube feeds*. Journal of Pediatric Gastroenterology and Nutrition, 1998. **27**(July): 53-56.
225. Walkowiak, J., D. Sands, A. Nowakowska, et al., *Early decline of pancreatic function in cystic fibrosis patients with class 1 or 2 CFTR mutations*. Journal of Pediatric Gastroenterology & Nutrition, 2005. **40**(2): 199-201.
226. Borowitz, D.S., R.J. Grand, and P.R. Durie, *Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy*. Journal of Pediatrics, 1995. **127**(5): 681-684.
227. Committee on the Safety of Medicines, *Report of the pancreatic enzymes working party*. 1995, Medicines Control Agency: London.
228. Schibli, S., P.R. Durie, and E.D. Tullis, *Proper usage of pancreatic enzymes*. Current Opinion in Pulmonary Medicine., 2002. **8**(6): 542-6.
229. Mehta, A., *Further comments on fibrosing colonopathy study*. Lancet, 2001. **358**(9292): 1546-7.
230. Leus, J., S. Van Biervliet, and E. Robberecht, *Detection and follow up of exocrine pancreatic insufficiency in cystic fibrosis: a review*. European Journal of Pediatrics, 2000. **159**(8): 563-8.
231. Rossipal, E., B. Paletta, and W. Mlekusch, *Zur Stuhlfettbestimmung bei Zöliakie*. Klinische Padiatrie, 1972. **184**(5): 385-8.
232. Couper, R. and P.R. Durie, *Pancreatic function tests*, in *Pediatric Gastrointestinal Disease*, W.A. Walker, P.R. Durie, J.R. Hamilton, J.A. Walker-Smith, and J.B. Watkins, Editors. 1991, B.C. Decker Inc.: Philadelphia.
233. Jeejeebhoy, K.N., S. Ahmad, and G. Kozak, *Determination of fecal fats containing both medium and long chain triglycerides and fatty acids*. Clinical Biochemistry, 1970. **3**(2): 157-63.
234. Losowsky, M.S., B.E. Walker, and J. Kelleher, *Assessment of fat absorption*, in *Malabsorption in clinical practice*. 1974, Churchill Livingstone: Edinburgh, Scotland. p. 85-86.
235. Anderson, C.M., V. Burke, and M. Gracey, *The exocrine pancreas: development, physiology and disease*, in *Paediatric gastroenterology, 2nd edn*. 1987, Blackwell: Melbourne. p. 456-502.
236. Phuapradit, P., A. Narang, P. Mendonca, D.A. Harris, and J.D. Baum, *The steatocrit: a simple method for estimating stool fat content in newborn infants*. Archives of Disease in Childhood, 1981. **56**(9): 725-7.
237. Amann, S.T., S.A. Josephson, and P.P. Toskes, *Acid steatocrit: a simple, rapid gravimetric method to determine steatorrhea*. American Journal of Gastroenterology, 1997. **92**(12): 2280-4.
238. Jedlicka-Kohler, I., M. Gotz, and I. Eichler, *Parents' recollection of the initial communication of the diagnosis of cystic fibrosis*. Pediatrics, 1996. **97**(2): 204-209.
239. Koletzko, S. and D. Reinhardt, *Nutritional challenges of infants with cystic fibrosis*. Early Human Development, 2001. **65 Suppl**: S53-61.
240. Parker, E.M., B.P. O'Sullivan, J.C. Shea, M.M. Regan, and S.D. Freedman, *Survey of breast-feeding practices and outcomes in the cystic fibrosis population*. Pediatric Pulmonology, 2004. **37**(4): 362-7.
241. Spieth, L.E., L.J. Stark, M.J. Mitchell, et al., *Observational assessment of family functioning at mealtime in preschool children with cystic fibrosis*. Journal of Pediatric Psychology, 2001. **26**(4): 215-24.
242. Buchdahl, R.M., C. Fulleylove, J.L. Marchant, J.O. Warner, and M.J. Brueton, *Energy and nutrient intakes in cystic fibrosis*. Archives of Disease in Childhood, 1989. **64**(3): 373-8.
243. Richter, T., C. Meier, K. Steppberger, G. Knorrek, and T. Lietz, *Experiences with enteral nutrition of patients with cystic fibrosis (CF) via a percutaneous endoscopic gastrostomy (PEG)*. Klinische Padiatrie, 2001. **213**(6): 325-8.
244. Stapleton, D.R., L.C. Gurrin, S.R. Zubrick, S.R. Silburn, J.L. Sherriff, and P.D. Sly, *The effect of Go and Grow with CF on the nutrition and pancreatic enzyme knowledge of children with cystic fibrosis*. Australian Journal of Nutrition and Dietetics, 2001.
245. Johannesson, M., C. Gottlieb, and L. Hjelte, *Delayed puberty in girls with cystic fibrosis despite good clinical status*. Pediatrics, 1997. **99**(1): 29-34.
246. Boyle, M.P., Z. Farukhi, and M.L. Nosky, *Strategies for improving transition to adult cystic fibrosis care, based on patient and parent views*. Pediatric Pulmonology, 2001. **32**(6): 428-36.

247. Zack, J., C.P. Jacobs, P.M. Keenan, et al., *Perspectives of patients with cystic fibrosis on preventive counseling and transition to adult care*. Pediatric Pulmonology, 2003. **36**(5): 376-83.
248. McKelvey, J. and M. Borgersen, *Family development and the use of diabetes groups: experience with a model approach*. Patient Education and Counseling, 1990. **16**: 61-67.
249. Stark, L.J., M.M. Mulvihill, E. Jelalian, et al., *Descriptive analysis of eating behaviour in school-age children with cystic fibrosis and healthy control children*. Pediatrics, 1997. **99**(5): 665-671.
250. Patterson, J.M., J. Budd, D. Goetz, and W.J. Warwick, *Family correlates of a 10-year pulmonary health trend in cystic fibrosis*. Pediatrics, 1993. **91**(2): 383-389.
251. Stapleton, D., *Development, implementation and evaluation of a nutrition education and behaviour program for children with cystic fibrosis*, in *School of Public Health*. 2001, Curtin University of Technology: Perth.
252. Glanz, K. and B.K. Rimer, *Theory at a glance: a guide for health promotion practice*. 1995, Bethesda US Department of Health and Human Services: National Institute for Health. 22-5.
253. Bernard, R.S. and L.L. Cohen, *Increasing adherence to cystic fibrosis treatment: a systematic review of behavioral techniques*. Pediatric Pulmonology, 2004. **37**(1): 8-16.
254. Poustie, V.J., R.M. Watling, and R.L. Smyth, *Oral protein-energy supplements for children with chronic disease: systematic review*. Proceedings of the Nutrition Society, 2003. **62**(4): 801-6.
255. Smyth, R. and S. Walters, *Oral calorie supplements for cystic fibrosis*. Cochrane Database of Systematic Reviews, 2000(2): CD000406.
256. Lees, C.M. and R.L. Smyth, *The current management of cystic fibrosis*. International Journal of Clinical Practice, 2000. **54**(3): 171-9.
257. Poustie, V.J., J.E. Russell, R.M. Watling, D. Ashby, R.L. Smyth, and CALICO Trial Collaborative Group, *Oral protein energy supplements for children with cystic fibrosis: CALICO multicentre randomised controlled trial*. BMJ, 2006. **332**(7542): 632-636.
258. Marchand, V., S.S. Baker, T.J. Stark, and R.D. Baker, *Randomized, double-blind, placebo-controlled pilot trial of megestrol acetate in malnourished children with cystic fibrosis*. Journal of Pediatric Gastroenterology and Nutrition, 2000. **31**(3): 264-9.
259. Homnick, D.N., B.D. Homnick, A.J. Reeves, J.H. Marks, R.S. Pimentel, and S.K. Bonnema, *Cyproheptadine is an effective appetite stimulant in cystic fibrosis*. Pediatric Pulmonology, 2004. **38**(2): 129-34.
260. Hardin, D.S., K.J. Ellis, M. Dyson, J. Rice, R. McConnell, and D.K. Seilheimer, *Growth hormone improves clinical status in prepubertal children with cystic fibrosis: results of a randomized controlled trial*. Journal of Pediatrics, 2001. **139**(5): 636-42.
261. Loprinzi, C.L., *Management of cancer anorexia/cachexia*. Supportive Care in Cancer, 1995. **3**(2): 120-2.
262. Raff, H., *Neonatal dexamethasone therapy: short- and long-term consequences*. Trends in Endocrinology and Metabolism, 2004. **15**(8): 351-2.
263. Oliver, M.R., R.G. Heine, C.H. Ng, E. Volders, and A. Olinsky, *Factors affecting clinical outcome in gastrostomy-fed children with cystic fibrosis*. Pediatric Pulmonology, 2004. **37**(4): 324-9.
264. Erskine, J.M., C.D. Lingard, M.K. Sontag, and F.J. Accurso, *Enteral nutrition for patients with cystic fibrosis: comparison of a semi-elemental and nonelemental formula*. Journal of Pediatrics, 1998. **132**(2): 265-9.
265. Liposky, J.M. and L.D. Nelson, *Ventilatory response to high caloric loads in critically ill patients*. Critical Care Medicine, 1994. **22**(5): 796-802.
266. Kane, R.E., P.J. Hobbs, and P.G. Black, *Comparison of low, medium, and high carbohydrate formulas for nighttime enteral feedings in cystic fibrosis patients*. JPEN. Journal of Parenteral and Enteral Nutrition, 1990. **14**(1): 47-52.
267. Talpers, S.S., D.J. Romberger, S.B. Bunce, and S.K. Pingleton, *Nutritionally associated increased carbon dioxide production. Excess total calories vs high proportion of carbohydrate calories*. Chest, 1992. **102**(2): 551-5.
268. Bond, P. and D. Moss, *Best practice in nasogastric and gastrostomy feeding in children*. Nursing Times, 2003. **99**(33): 28-30.
269. Anonymous, *Section V: Administration of specialized nutrition support (from Guidelines for the use of parenteral and enteral nutrition)*. JPEN. Journal of Parenteral and Enteral Nutrition, 2002. **26**(1): SA1-SA6.
270. Lester, L.A., R.M. Rothberg, G. Dawson, A.L. Lopez, and Z. Corpuz, *Supplemental parenteral nutrition in cystic fibrosis*. JPEN. Journal of Parenteral and Enteral Nutrition, 1986. **10**(3): 289-295.
271. Mansell, A.L., J.C. Anderson, C.R. Muttart, et al., *Short-term effects of total parenteral nutrition in children with cystic fibrosis*. Journal of Pediatrics, 1984. **104**(5): 700-705.

272. Allen, E.D., A.B. Mick, J. Nicol, and K.S. McCoy, *Prolonged parenteral nutrition for cystic fibrosis patients*. Nutrition in Clinical Practice, 1995. **10**(2): 73-79.
273. Littlewood, J.M., *Gastrointestinal complications in cystic fibrosis*. Journal of the Royal Society of Medicine, 1992. **85 Suppl 19**: 13-9.
274. Taylor, C.J., P.S. Baxter, J. Hardcastle, and P.T. Hardcastle, *Absence of secretory response in jejunal biopsy samples from children with cystic fibrosis*. Lancet, 1987. **2**(8550): 107-8.
275. Andersen, H.O., K. Hjelt, E. Waever, and K. Overgaard, *The age-related incidence of meconium ileus equivalent in a cystic fibrosis population: the impact of high-energy intake*. Journal of Pediatric Gastroenterology and Nutrition, 1990. **11**(3): 356-60.
276. Hodson, M.E., M.B. Mearns, and J.C. Batten, *Meconium ileus equivalent in adults with cystic fibrosis of pancreas: a report of six cases*. BMJ, 1976. **2**(6039): 790-1.
277. Rubinstein, S., R. Moss, and N. Lewiston, *Constipation and meconium ileus equivalent in patients with cystic fibrosis*. Pediatrics, 1986. **78**(3): 473-479.
278. Ramsden, W.H., E.F. Moya, and J.M. Littlewood, *Colonic wall thickness, pancreatic enzyme dose and type of preparation in cystic fibrosis*. Archives of Disease in Childhood, 1998. **79**: 339-343.
279. Davidson, A.G.F., *Gastrointestinal and pancreatic disease in cystic fibrosis*, in *Cystic Fibrosis (2nd edition)*, M.E. Hodson and D.M. Geddes, Editors. 2000, Arnold: London. p. 261-288.
280. Salvatore, S. and Y. Vandenplas, *Gastro-oesophageal reflux disease and motility disorders*. Best Practice and Research Clinical Gastroenterology, 2003. **17**(2): 163-179.
281. Button, B.M., R.G. Heine, A.G. Catto-Smith, P.D. Phelan, and A. Olinsky, *Postural drainage and gastro-oesophageal reflux in infants with cystic fibrosis*. Archives of Disease in Childhood, 1997. **76**(2): 148-50.
282. Button, B.M., S. Roberts, T. Kotsimbos, J. Wilson, and M. Bailey, *Symptomatic versus asymptomatic (silent) gastroesophageal reflux (GER) in adults with cystic fibrosis: comparison of the usefulness of a structured symptom questionnaire to 24hr esophageal pH monitoring in identifying GER*. Pediatric Pulmonology, 2002. **Supplement 24**: 301.
283. Ledson, M.J., J. Tran, and M.J. Walshaw, *Prevalence and mechanisms of gastro-oesophageal reflux in adult cystic fibrosis patients*. Journal of the Royal Society of Medicine, 1998. **91**(1): 7-9.
284. Malfroot, A. and I. Dab, *New insights on gastro-oesophageal reflux in cystic fibrosis by longitudinal follow up*. Archives of Disease in Childhood, 1991. **66**(11): 1339-45.
285. Vinocur, C.D., L. Marmon, D.V. Schidlow, and W.H. Weintraub, *Gastroesophageal reflux in the infant with cystic fibrosis*. American Journal of Surgery, 1985. **149**(1): 182-6.
286. Scott, R.B., E.V. O'Loughlin, and D.G. Gall, *Gastroesophageal reflux in patients with cystic fibrosis*. Journal of Pediatrics, 1985. **106**(2): 223-7.
287. Gregory, P.C., *Gastrointestinal pH, motility/transit and permeability in cystic fibrosis*. Journal of Pediatric Gastroenterology and Nutrition, 1996. **23**(5): 513-23.
288. Cucchiara, S., F. Santamaria, M.R. Andreotti, et al., *Mechanisms of gastro-oesophageal reflux in cystic fibrosis*. Archives of Disease in Childhood, 1991. **66**(5): 617-22.
289. Stringer, D.A., A. Sprigg, E. Juodis, et al., *The association of cystic fibrosis, gastroesophageal reflux, and reduced pulmonary function*. Canadian Association of Radiologists Journal, 1988. **39**(2): 100-2.
290. Galmiche, J.P., *Gastro-oesophageal reflux: does it matter what you eat?* Gut, 1998. **42**(3): 318-9.
291. Button, B.M., R.G. Heine, A.G. Catto-Smith, and P.D. Phelan, *Postural drainage in cystic fibrosis: is there a link with gastro-oesophageal reflux?* Journal of Paediatrics and Child Health, 1998. **34**(4): 330-4.
292. Meining, A. and M. Classen, *The role of diet and lifestyle measures in the pathogenesis and treatment of gastroesophageal reflux disease*. American Journal of Gastroenterology, 2000. **95**(10): 2692-2697.
293. Dent, J., J. Brun, A.M. Fendrick, et al., *An evidence-based appraisal of reflux disease management - the Genval Workshop Report*. Gut, 1999. **44** (suppl 2): S1-S16.
294. Gottrand, F. and L. Michaud, *Percutaneous endoscopic gastrostomy and gastroesophageal reflux: are we correctly addressing the question?* Journal of Pediatric Gastroenterology and Nutrition, 2002. **35**(1): 22-24.
295. Heyland, D., J. Drover, S. Macdonald, F. Novak, and M. Lam, *Effect of postpyloric feeding on gastroesophageal reflux and microaspiration: results of a randomised controlled trial*. Critical Care Medicine, 2001. **29**(8): 1495-1501.
296. Sokol, R.J. and P.R. Durie, *Recommendations for management of liver and biliary tract disease in cystic fibrosis*. Cystic Fibrosis Foundation Hepatobiliary Disease Consensus Group. Journal of Pediatric Gastroenterology and Nutrition, 1999. **28 Suppl 1**: S1-13.

297. Colombo, C., M.G. Apostolo, M. Ferrari, et al., *Analysis of risk factors for the development of liver disease associated with cystic fibrosis*. Journal of Pediatrics, 1994. **124**(3): 393-9.
298. Colombo, C., P.M. Battezzati, A. Crosignani, et al., *Liver disease in cystic fibrosis: A prospective study on incidence, risk factors, and outcome*. Hepatology, 2002. **36**(6): 1374-82.
299. Merli, M., S. Bertasi, R. Servi, et al., *Effect of a medium dose of ursodeoxycholic acid with or without taurine supplementation on the nutritional status of patients with cystic fibrosis: a randomized, placebo-controlled, crossover trial*. Journal of Pediatric Gastroenterology and Nutrition, 1994. **19**(2): 198-203.
300. Cotting, J., M.J. Lentze, and J. Reichen, *Effects of ursodeoxycholic acid treatment on nutrition and liver function in patients with cystic fibrosis and longstanding cholestasis*. Gut, 1990. **31**(8): 918-21.
301. Colombo, C., D. Costantini, A. Rocchi, et al., *Effects of liver transplantation on the nutritional status of patients with cystic fibrosis*. Transplant International, 2005. **18**(2): 246-55.
302. Durno, C., M. Corey, J. Zielenski, E. Tullis, L.C. Tsui, and P. Durie, *Genotype and phenotype correlations in patients with cystic fibrosis and pancreatitis.[see comment]*. Gastroenterology, 2002. **123**(6): 1857-64.
303. Vanderbruggen, K., K. De Waele, S. Van Biervliet, G. Van Der Cruyssen, and E. Robberecht, *Cystic fibrosis: an unusual cause of chronic pancreatitis*. Acta Gastroenterologica Belgica, 2003. **66**(3): 260-2.
304. Rolles, C.J., *Gastroenterology*, in *Practical Guidelines for Cystic Fibrosis Care*, C.M. Hill, Editor. 1998, Churchill Communications: Europe.
305. Virgilis, D., L. Rivkin, A. Samueloff, et al., *Cystic fibrosis, pregnancy, and recurrent, acute pancreatitis*. Journal of Pediatric Gastroenterology and Nutrition, 2003. **36**(4): 486-8.
306. Slaff, J., D. Jacobson, C.R. Tillman, C. Curington, and P. Toskes, *Protease-specific suppression of pancreatic exocrine secretion*. Gastroenterology, 1984. **87**(1): 44-52.
307. Lannig, S., A. Hansen, B. Thorsteinsson, J. Nerup, and C. Koch, *Glucose tolerance in patients with cystic fibrosis: five year prospective study*. BMJ, 1995. **311**(7006): 655-9.
308. Lannig, S., B. Thorsteinsson, C. Lund-Andersen, J. Nerup, P.O. Schiøtz, and C. Koch, *Diabetes mellitus in Danish cystic fibrosis patients: prevalence and late diabetic complications*. Acta Paediatrica, 1994. **83**(1): 72-7.
309. Finkelstein, S.M., C.L. Wielinski, G.R. Elliott, et al., *Diabetes mellitus associated with cystic fibrosis*. Journal of Pediatrics, 1988. **112**(3): 373-7.
310. Matson, A.G., K.M. Herd, S.C. Bell, and J. Bunting. *Cystic fibrosis related diabetes - prevalence and management at an Australian CF unit*. in *Sixth Australian and New Zealand Cystic Fibrosis Conference*. 2005. Adelaide, Australia.
311. Moran, A., L. Doherty, X. Wang, and W. Thomas, *Abnormal glucose metabolism in cystic fibrosis*. Journal of Pediatrics, 1998. **133**(1): 10-17.
312. Moran, A., C. Milla, R. Ducret, and K.S. Nair, *Protein metabolism in clinically stable adult cystic fibrosis patients with abnormal glucose tolerance*. Diabetes, 2001. **50**(6): 1336-43.
313. Milla, C.E., W.J. Warwick, and A. Moran, *Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline*. American Journal of Respiratory and Critical Care Medicine, 2000. **162**(3 Pt 1): 891-5.
314. Lannig, S., B. Thorsteinsson, J. Nerup, and C. Koch, *Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis*. European Journal of Pediatrics, 1992. **151**(9): 684-7.
315. Lannig, S., B. Thorsteinsson, G. Erichsen, J. Nerup, and C. Koch, *Glucose tolerance in cystic fibrosis*. Archives of Disease in Childhood, 1991. **66**(5): 612-6.
316. Dobson, L., C.D. Sheldon, and A.T. Hattersley, *Understanding cystic-fibrosis-related diabetes: best thought of as insulin deficiency?* Journal of the Royal Society of Medicine, 2004. **97** Suppl **44**: 26-35.
317. Lannig, S., B. Thorsteinsson, J. Nerup, and C. Koch, *Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections*. Acta Paediatrica, 1994. **83**(8): 849-53.
318. Rosenecker, J., I. Eichler, H. Barmeier, and H. von der Hardt, *Diabetes mellitus and cystic fibrosis: comparison of clinical parameters in patients treated with insulin versus oral glucose-lowering agents*. Pediatric Pulmonology, 2001. **32**(5): 351-5.
319. Zipf, W., *Therapeutic options for treatment of diabetes mellitus in cystic fibrosis*. Pediatric Pulmonology. Supplement, 1995. **5**: 111-114.
320. Mackie, A.D., S.J. Thornton, and F.P. Edenborough, *Cystic fibrosis-related diabetes*. Diabetic Medicine, 2003. **20**(6): 425-36.

321. National Health and Medical Research Council, *Clinical practice guidelines: Type 1 diabetes in children and adolescents*. 2005, Commonwealth of Australia: Canberra, Australia.
322. The Diabetes Control and Complications Trial Research Group, *The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus*. *New England Journal of Medicine*, 1993. **329**(14): 977-86.
323. UK Prospective Diabetes Study (UKPDS) Group, *Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)*. *Lancet*, 1998. **352**(9131): 837-53.
324. Yung, B., M. Kemp, J. Hooper, and M.E. Hodson, *Diagnosis of cystic fibrosis related diabetes: a selective approach in performing the oral glucose tolerance test based on a combination of clinical and biochemical criteria*. *Thorax*, 1999. **54**(1): 40-3.
325. Rodman, H.M., C.F. Doershuk, and J.M. Roland, *The interaction of 2 diseases: diabetes mellitus and cystic fibrosis*. *Medicine*, 1986. **65**(6): 389-97.
326. Sullivan, M.M. and C.R. Denning, *Diabetic microangiopathy in patients with cystic fibrosis*. *Pediatrics*, 1989. **84**(4): 642-7.
327. Elkin, S.L., L. Williams, M. Moore, M.E. Hodson, and O.M. Rutherford, *Relationship of skeletal muscle mass, muscle strength and bone mineral density in adults with cystic fibrosis*. *Clinical Science*, 2000. **99**(4): 309-14.
328. Elkin, S.L., A. Fairney, S. Burnett, et al., *Vertebral deformities and low bone mineral density in adults with cystic fibrosis: a cross-sectional study*. *Osteoporosis International*, 2001. **12**: 366-372.
329. WHO, *Assessment of fracture risk and its application to screening for postmenopausal osteoporosis*. WHO Technical Report Series, 1994. **843**: 1-129.
330. Aris, R.M., G.E. Lester, and D.A. Ontjes, *Treatment of bone disease in cystic fibrosis*. *Current Opinion in Pulmonary Medicine*, 2004. **10**(6): 524-530.
331. Aris, R.M., J.B. Renner, A.D. Winders, et al., *Increased rate of fractures and severe kyphosis: sequelae of living into adulthood with cystic fibrosis*. *Annals of Internal Medicine*, 1998. **128**: 186-193.
332. Aris, R.M., I.P. Neuringer, M.A. Weiner, T.M. Egan, and D. Ontjes, *Severe osteoporosis before and after lung transplantation*. *Chest*, 1996. **109**(5): 1176-83.
333. Donovan, D.S., A. Papadopoulos, R.B. Staron, et al., *Bone mass and vitamin D deficiency in adults with advanced cystic fibrosis lung disease*. *American Journal of Respiratory and Critical Care Medicine*, 1998. **158**: 1892-1899.
334. Aris, R.M., A. Stephens, D.A. Ontjes, et al., *Adverse alterations in bone metabolism are associated with lung infection in cystic fibrosis*. *American Journal of Respiratory and Critical Care Medicine*, 2000. **162**: 1674-1678.
335. Bhudhikanok, G.S., J. Lim, R. Marcus, A. Harkins, R.B. Moss, and L.K. Bachrach, *Correlates of osteopaenia in patients with cystic fibrosis*. *Pediatrics*, 1996. **97**: 103-111.
336. Haworth, C.S., P.L. Selby, A.W. Horrocks, E.B. Mawer, J.E. Adams, and A.K. Webb, *A prospective study of change in bone mineral density over one year in adults with cystic fibrosis*. *Thorax*, 2002. **57**(8): 719-723.
337. Greer, R.M., P.W. Francis, J.A. Batch, and P.K. O'Rourke, *Bone density is lower in males with cystic fibrosis than in females: a meta-analysis*. *Pediatric Pulmonology*, 2004. **Supplement 27**: 325.
338. Aris, R.M., G.E. Lester, M. Caminiti, et al., *Efficacy of alendronate in adults with cystic fibrosis with low bone density*. *American Journal of Respiratory and Critical Care Medicine*, 2004. **169**(1): 77-82.
339. Haworth, C.S., *Treatment of cystic fibrosis bone disease*. *Pediatric Pulmonology*, 2002. **Supplement 24**: 180-181.
340. Conway, S.P., B. Oldroyd, A. Morton, J.G. Truscott, and D.G. Peckham, *Effect of oral bisphosphonates on bone mineral density and body composition in adult patients with cystic fibrosis: a pilot study*. *Thorax*, 2004. **59**(8): 699-703.
341. Ebeling, P.R., *Megadose therapy for vitamin D deficiency*. *Medical Journal of Australia*, 2005. **183**(1): 4-5.
342. Reid, I.R., R.W. Ames, M.C. Evans, G.D. Gamble, and S.J. Sharpe, *Effect of calcium supplementation on bone loss in postmenopausal women*. *New England Journal of Medicine*, 1993. **328**: 460-464.
343. Dawson-Hughes, B., S. Harris, E.A. Krall, and G.E. Dallal, *Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older*. *New England Journal of Medicine*, 1997. **337**: 670-676.

344. Jankelson, D., M. Robinson, S. Parsons, P. Torzillo, B. Peat, and P. Bye, *Cystic fibrosis and pregnancy*. Australian and New Zealand Journal of Obstetrics and Gynaecology, 1998. **38**(2): 180-4.
345. Kent, N.E. and D.F. Farquharson, *Cystic fibrosis in pregnancy*. CMAJ, 1993. **149**(6): 809-13.
346. Geddes, D.M., *Cystic fibrosis and pregnancy*. Journal of the Royal Society of Medicine, 1992. **85 Suppl 19**: 36-7.
347. Cohen, L.F., P.A. di Sant'Agnes, and J. Friedlander, *Cystic fibrosis and pregnancy. A national survey*. Lancet, 1980. **2**(8199): 842-4.
348. Edenborough, F.P., W.E. Mackenzie, and D.E. Stableforth, *The outcome of 72 pregnancies in 55 women with cystic fibrosis in the United Kingdom 1977-1996*. British Journal of Obstetrics and Gynaecology, 2000. **107**(2): 254-61.
349. Goss, C.H., G.D. Rubinfeld, K. Otto, and M.L. Aitken, *The effect of pregnancy on survival in women with cystic fibrosis*. Chest, 2003. **124**(4): 1460-8.
350. Rothman, K.J., L.L. Moore, M.R. Singer, U.S. Nguyen, S. Mannino, and A. Milunsky, *Teratogenicity of high vitamin A intake.[see comment]*. New England Journal of Medicine, 1995. **333**(21): 1369-73.
351. Food Standards Australia and New Zealand, *Fact sheet: folate*. 1999b.
352. Kendall, P., L.C. Medeiros, V. Hillers, G. Chen, and S. DiMascola, *Food handling behaviors of special importance for pregnant women, infants and young children, the elderly, and immune-compromised people*. Journal of the American Dietetic Association, 2003. **103**(12): 1646-9.
353. Food Standards Australia and New Zealand, *Fact sheet :listeria*. 1999a.
354. Johannesson, M., *Effects of pregnancy on health: certain aspects of importance for women with cystic fibrosis*. Journal of Cystic Fibrosis, 2002. **1**(1): 9-12.
355. Hilman, B.C., M.L. Aitken, and M. Constantinescu, *Pregnancy in patients with cystic fibrosis*. Clinical Obstetrics and Gynecology, 1996. **39**(1): 70-86.
356. Eggermont, E., *Gastrointestinal manifestations in cystic fibrosis*. European Journal of Gastroenterology and Hepatology, 1996. **8**(8): 731-8.
357. Trulock, E.P., L.B. Edwards, D.O. Taylor, M.M. Boucek, B.M. Keck, and M.I. Hertz, *The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult lung and heart-lung transplant report—2004*. Journal of Heart and Lung Transplantation, 2004. **23**(7): 804-15.
358. Madill, J., C. Gutierrez, J. Grossman, et al., *Nutritional assessment of the lung transplant patient: body mass index as a predictor of 90-day mortality following transplantation*. Journal of Heart and Lung Transplantation, 2001. **20**(3): 288-96.
359. Schwebel, C., I. Pin, D. Barnoud, et al., *Prevalence and consequences of nutritional depletion in lung transplant candidates*. European Respiratory Journal, 2000. **16**(6): 1050-5.
360. Snell, G.I., K. Bennetts, J. Bartolo, et al., *Body mass index as a predictor of survival in adults with cystic fibrosis referred for lung transplantation*. Journal of Heart and Lung Transplantation, 1998. **17**: 1097-1103.
361. Sharples, L., T. Hamaway, C. Dennis, N. Caine, T. Higenbottam, and J. Wallwork, *Prognosis of patients with cystic fibrosis awaiting heart and lung transplantation*. Journal of Heart and Lung Transplantation, 1996. **12**: 669-674.
362. American Society for Transplant Physicians, American Thoracic Society, European Respiratory Society, and International Society for Heart and Lung Transplantation, *International Guidelines for the Selection of Lung Transplant Candidates*. American Journal of Respiratory and Critical Care Medicine, 1998. **158**(1): 335-339.
363. Egan, J.J., A.A. Woodcock, and A.K. Webb, *Management of cystic fibrosis before and after lung transplantation*. Journal of the Royal Society of Medicine, 1997. **90 Suppl 31**: 47-58.
364. Naon, H., S. Hack, M.T. Shelton, R.C. Gotthoffer, and D. Gozal, *Resting energy expenditure. Evolution during antibiotic treatment for pulmonary exacerbation in cystic fibrosis*. Chest, 1993. **103**(6): 1819-25.
365. Tynan, C. and J.M. Hasse, *Current Nutrition Practices in Adult Lung Transplantation*. Nutrition in Clinical Practice, 2004. **19**: 587-596.
366. Hasse, J.M., *Diet therapy for organ transplantation. A problem-based approach*. Nursing Clinics of North America, 1997. **32**(4): 863-80.
367. Pahwa, N. and A. Hedberg, *Adult Heart and Lung Transplantation*, in *Comprehensive Guide to Transplant Nutrition*, J.M. Hasse and L.S. Blue, Editors. 2002, American Dietetic Association: Chicago IL. p. 31-43.

368. Davies, B.W., A.R. Watson, J.E. Coleman, and C.H. Rance, *Do gastrostomies close spontaneously? A review of the fate of gastrostomies following successful renal transplantation in children*. *Pediatric Surgery International*, 2001. **17**(4): 326-8.
369. Stephenson, A., M. Brotherwood, R. Robert, et al., *Increased vitamin A and E levels in adult cystic fibrosis patients after lung transplantation*. *Transplantation*, 2005. **79**(5): 613-5.
370. Young, L.R., D. Hadjiliadis, R.D. Davis, and S.M. Palmer, *Lung transplantation exacerbates gastroesophageal reflux disease*. *Chest*, 2003. **124**(5): 1689-93.
371. Gilljam, M., C. Chaparro, E. Tullis, C. Chan, S. Keshavjee, and M. Hutcheon, *GI complications after lung transplantation in patients with cystic fibrosis*. *Chest*, 2003. **123**(1): 37-41.
372. Chan, L.N., *Drug-nutrient interactions in transplant recipients*. *Journal of Parenteral and Enteral Nutrition*, 2001. **25**(3): 132-41.
373. Tsang, V.T., A. Johnston, F. Heritier, N. Leaver, M.E. Hodson, and M. Yacoub, *Cyclosporin pharmacokinetics in heart-lung transplant recipients with cystic fibrosis. Effects of pancreatic enzymes and ranitidine*. *European Journal of Clinical Pharmacology*, 1994. **46**(3): 261-5.
374. Bartholomew, L., G. Parcel, D. Seilheimer, D. Czyzewski, S. Spinelli, and B. Congdon, *Development of a health education program to promote the self-management of cystic fibrosis*. *Health Education Quarterly*, 1991. **18**(Winter): 429-443.
375. Eigen, H., N.M. Clark, and J.M. Wolle, *Clinical-behavioural aspects of cystic fibrosis: directions for future research*. *American Review of Respiratory Diseases*, 1987. **136**: 1509-1513.
376. Gilbertson, H. and E. Volders. *Nutrition education for children with chronic illness*. in *1994 Dietitians Association of Australia Conference*. 1994.
377. Koocher, G.P., M.L. McGrath, and L.J. Gudas, *Typologies of nonadherence in cystic fibrosis*. *Developmental and Behavioural Pediatrics*, 1990. **11**(6): 353-358.
378. McCulloch, D.K., R.D. Mitchell, J. Ambler, and R.B. Tattersall, *Influence of imaginative teaching of diet on compliance and metabolic control in insulin dependent diabetes*. *British Medical Journal*, 1983. **287**(17): 1858-1861.
379. Perry, C., R. Luepker, D. Murray, et al., *Parent involvement with children's health promotion: a one-year follow-up of the Minnesota home team*. *Health Education Quarterly*, 1989. **16**(2): 171-180.
380. Sallis, J., *Improving adherence to pediatric therapeutic regimens*. *Pediatric Nursing*, 1985. **11**(March/April): 118-120, 148.