cystic fibrosis nutrition
AUSTRALIA · NEW ZEALAND

The Thoracic Society of Australia & New Zealand
LEADERS IN LUNG HEALTH

NUTRITION GUIDELINES FOR CYSTIC FIBROSIS

in Australia and New Zealand

August 2017

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Disclaimers

The primary custodian of the 'Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand Project' is the TSANZ. The following professional organisations were collaborators in the creation of this document:

- Dietitians Association of Australia (DAA)
- Dietitians New Zealand (DNZ)
- Cystic Fibrosis Australia (CFA)
- Cystic Fibrosis Association of New Zealand (CFANZ)

This document is written as a general guide to practice only and does not discount individualised assessment and advice, by a suitably qualified clinician. Content within this publication was accurate at the time of publication.

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NHMRC is satisfied that the guideline recommendations are systematically derived, based on the identification and synthesis of the best available scientific evidence, and developed for health professionals practising in an Australian health care setting.

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Additional information about the roles of the dietitian steering group and interdisciplinary clinical expert committee, including methods for addressing conflicts of interests and declarations of conflicts of interest, can be found in the accompanying Administration Report.

IN MEMORIAM

We are honoured to dedicate this project to the memory of Anne-Maree Bosch. Every project has people on the side-lines – those people who cheer us on, and those who open doors to make things happen. For a generation of people working in CF, Anne-Maree was a wonderfully generous colleague and friend. Her enthusiasm, willingness to go above and beyond, and commitment, capture the spirit of this project.

CONTENTS

FOREWORD

Cystic Fibrosis Australia (CFA) whole-heartedly supports the development of nutrition guidelines for cystic fibrosis (CF) in Australia and New Zealand. In recent years nutrition has come to the forefront as a successful health strategy to improve the lives of people with cystic fibrosis. CFA's data registry shows the value of nutritional guidance and advice and therefore CFA is keen to see best practice 'rolled out' across Australia and New Zealand.

Australia and NZ are wide and diverse countries, and people with CF should have access to the best health professions and strategies where ever they live. The Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand will ensure the provision of quality, up to date information about nutrition management and importantly if people move to another CF Centre or state they will have consistency of care and guidance.

Cystic Fibrosis Nutrition - Australia New Zealand are a passionate group of dietitians, with representatives from all CF specialist centres and outreach services across Australia and New Zealand - they constantly impress care teams and the CF community with their innovative approach to CF nutrition. Cystic Fibrosis Australia thanks these dedicated dietitians for their commitment to best practice and we look forward to supporting their efforts to get exceptional national consistency in dietetics across Australia and New Zealand.

Nettie Burke
Chief Executive Officer
Cystic Fibrosis Australia

ABBREVIATIONS AND ACRONYMS

ALA = alpha-linoleic acid
BMI = body mass index
CCRS = Clinical Care and Resources Subcommittee (TSANZ)
CDC = Centers for Disease Control
CF = cystic fibrosis
CFA = Cystic Fibrosis Australia
CFNZ = Cystic Fibrosis New Zealand
CRP = C-reactive protein
DAA = Dietitians Association of Australia
DHA = docosahexaenoic acid
DIOS = distal intestinal obstruction syndrome
DNZ = Dietitians New Zealand
DXA = dual x-ray absorptiometry
EAR = estimated Average Requirement
FEV_1 = forced expiratory volume in 1 second
FFM = fat free mass
GOR = gastro-oesophageal reflux
HbA1c = glycated haemoglobin
HDL = high-density lipoprotein
IV = intravenous
LDL = low-density lipoprotein
MUFA = monounsaturated
NODAT = new onset diabetes after transplant
NHMRC = National Health and Medical Research Council
NZ = New Zealand
ONS = oral nutrition supplement
PERT = pancreatic enzyme replacement therapy
PUFA = polyunsaturated fatty acid
RDI = recommended dietary intake
RDI = recommended dietary intake
REE = resting energy expenditure
SFA = saturated fatty acid
TFA = trans-fatty acid
TSANZ = Thoracic Society of Australia and New Zealand
UK = United Kingdom
UL = upper Level
USA = United States of America
WHO = World Health Organization

EXECUTIVE SUMMARY

Optimising growth and nutrition in people with cystic fibrosis (CF) has been shown to positively influence lung function and survival. The '2017 *Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand*' (herein referred to as *'2017 Guidelines'*) is a planned update of previously published guidelines - The '*2006 Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis*'[1]. This edition acknowledges and incorporates new topic areas including the nutritional implications of new genetic modulatory therapies, the emergence of overweight and obesity in CF, and complementary nutritional therapies. An overview of dietitian prescribing in New Zealand (NZ) is also provided. This document was developed by a group of Australian and NZ dietitians experienced in CF care, with the assistance of an interdisciplinary clinical expert committee representing various other health professions and CF consumers. In total, 70 people from a total of 24 different CF centres in the 2 countries were involved in this project, see figure 1 below.

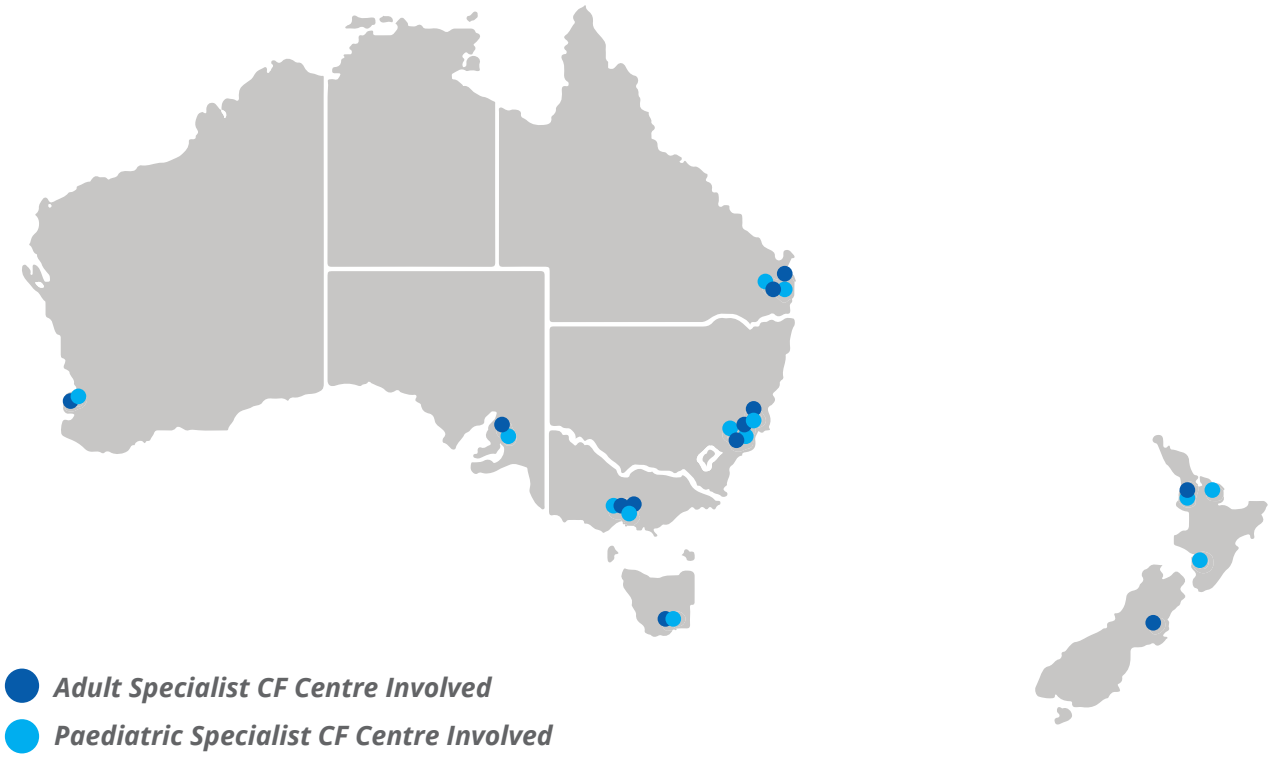

Figure 1. Specialist CF centres involved in the development of the guidelines

The key clinical question addressed is: ***"What is the role and scope of nutritional care in the management of CF?"***

Where possible, we have aimed to address specific clinical practice questions to help guide nutrition care. Details of the systematic review process used in the development of these guidelines are given in the technical report that accompanies this document.

While reading this guideline, it is important to remember the importance that people with CF and their families/carers play in attaining and maintaining optimal nutrition status. These are the people who live with the condition day-to-day and who are responsible for implementing nutrition interventions in the home environment. Individual needs and preferences need to be considered at all times.

MAJOR GUIDELINE THEMES

Below is a summary of the overarching recommendations made in the '2017 *Guidelines*'.

ASSESSMENT

- Assessment of anthropometric parameters should be conducted in children and adults at every clinic (Chapter 5).
  - It is becoming increasingly common to see people with CF who are overweight. Practitioners should screen for both undernutrition and overweight and obesity.
- Annual comprehensive nutrition assessments are strongly encouraged (Chapter 5).

INTERVENTION

- Newborn screening is standard practice in Australia and NZ; promotion of good nutrition should be commenced at diagnosis (Chapter 4).
- Interdisciplinary nutrition management is essential for people with CF (Chapter 4).
  - Liaise with a gastroenterologist, ideally with CF experience, for the management of common gastrointestinal co-morbidities (Chapter 11) e.g. distal intestinal obstruction syndrome (DIOS), constipation, gastro-oesophageal reflux (GOR) and liver disease.
  - Liaise with an endocrinologist, ideally with CF experience, for the management of CF-related diabetes (Chapter 12) and bone disease (Chapter 13).
- Diet recommendations for people with CF are moving closer to general population guidelines.
  - Aim to achieve and maintain optimal weight status and encourage people with CF to be physically active and choose amounts of nutritious foods and drinks to meet individual energy needs
    - There is a wide inter-individual range of energy requirements about 1.1 to 2 times reference intakes of the general population (Section 7.1).
    - A high energy/high fat diet will be especially beneficial for those people who are undernourished (Section 6.1).
  - Promote enjoyment of a wide variety of nutritious foods from all five food groups every day.
  - Encourage intake of foods containing unsaturated fats and omega-3 fatty acids.
  - Encourage, support and promote breastfeeding of infants diagnosed with CF. (Section 3.1).
- A high salt diet is recommended for most people with CF (Chapter 9).
- Routine supplementation of fat soluble vitamins (A, D, E, K) is encouraged, particularly in those who are pancreatic insufficient (Chapter 8).
- Pancreatic Enzyme Replacement Therapy (PERT) is recommended for all people who are pancreatic insufficient and should be taken with fat-containing foods (Chapter 10).
- Behavioural modification strategies (children) and nutrition education (children and adults) are evidence-based components of standard CF care (Chapter 6).
- Consider the use of oral supplements on an individual basis, the evidence does not support their routine use (Chapter 6).
- For people who are underweight long-term, enteral feeding should be considered by the interdisciplinary team. (Chapter 6).
- There is insufficient evidence to recommend routine supplementation of any complementary nutritional therapies (including probiotics, garlic, ginseng, curcumin, coconut oil) (Chapter 15).

MONITORING AND EVALUATION

Conduct regular and lifelong nutrition surveillance, with all aspects of nutrition and gastrointestinal status being reviewed (Chapter 5).

RECOMMENDATION TABLES

KEY: Q = question, R = recommendation (evidence based), PP = practice point (consensus)

Chapter 4 **Service Delivery**	
Q 4.1	**What is the level of dietetic service required for people with CF?**
R 4.1	Insufficient evidence to make a recommendation
PP 4.1	Dietetic staffing levels should follow the most recent country specific Standards for CF Care[2,3].

Chapter 5 **Nutrition Assessment**

No PICO questions were formulated for Chapter 5. This is an area of limited evidence specific to CF, with most international recommendations being formed by expert opinion.

Key Points

- Assessment of anthropometric parameters should be conducted in children and adults at every clinic – practitioners should screen for both under and over nutrition.
- Nutrition review by a dietitian is recommended at least four times a year as per the Australia and New Zealand Standard of care documents[2,3]. Deterioration in nutrition parameters should be detected early, before growth and pulmonary function are compromised.
- Annual comprehensive nutrition assessments are strongly encouraged. These should encompass a collation of anthropometric, dietary, biochemical and relevant clinical data.
- Levels of fat soluble vitamins (with associated tests to aid interpretation) should be routinely tested together as a group to aid interpretations of abnormal findings
- The following criteria are suggestive of optimal weight status:
  - Infants (0 to 24 months): weight-for-length ≥50th percentile using WHO growth charts
  - Children and Adolescents (2-18 years): BMI 50-85th percentile (if using CDC growth charts) or 50-91st percentile (if using WHO growth charts)
  - Adults: males BMI 23 - 27 kg/m^2, females BMI 22 - 27 kg/m^2
- The transition from WHO to CDC growth charts at 2 years can be difficult to interpret as weight and height percentiles do not correspond precisely (see Appendix B).
- Body composition measurements can further aid nutrition status evaluation. Practitioners should consider using body composition methods in people who are underweight, overweight or in those with unexplained weight changes.
- It is important to raise nutrition concerns with the interdisciplinary team early.
- Telehealth models of care are emerging and may augment face to face interdisciplinary reviews when more frequent dietetic monitoring and/or education is required.
- Where there is a shared care model, the responsibility for integrating nutrition assessment data and identifying nutrition diagnoses/nutrition problems must be clearly identified to ensure that early signs of undernutrition are detected.
- Food diary apps, allowing for electronic documentation of intake, are becoming more readily available. The Australia based app, *Easy Diet Diary*® allows people to manually enter intake or scan barcodes of packaged foods. When shared with the CF dietitian, intake can be quantified using computerised food composition software.

Chapter 6 **Nutrition Interventions**	
Behaviour Modification Strategies & Nutrition Education	
Q 6.1.1	**Compared to standard nutritional care, do behavioural interventions around food and mealtimes improve behaviours, diet variety, and weight or nutrition status in children with CF?**
R 6.1.1	GRADE B. Offer behavioural modification strategies to children at risk of/or with identified undernutrition. Conduct behavioural modification strategies in combination with nutrition education. [4-8]
Q 6.1.2	**When should behavioural interventions around food and mealtimes be considered for children with CF?**
R 6.1.2	GRADE C. Commence behavioural modification strategies early in life (i.e. during infancy or toddlerhood) and potentially continue throughout childhood. Offer the following strategies: • Differential attention (praise and ignoring) • Contingency management (child only receives a desired reward after they have eaten their meal and/or performed desired mealtime behaviours) • Self-monitoring of food intake (parents and/or child) • Parental limit setting (establishing clear expectations and consequences) [7,9,10]
PP 6.1.1 and 6.1.2	Behavioural modification strategies are a valuable component of standard paediatric CF care Strategies should be considered at a young age, before disruptive eating and mealtime behaviours become an ongoing issue. For best results, strategies should be conducted with nutrition education.
Appetite Stimulants & Growth Hormone	
Q 6.1.3	**Do appetite stimulants, megesterol acetate and cyproheptadine, improve nutritional status in CF?**
R 6.1.3	GRADE C. There is some evidence to suggest that appetite stimulants may improve weight and appetite for people with CF. However, the potential risk of adverse side effects and insufficient evidence means that routine use of appetite stimulants to improve nutritional status is not recommended. [11]
Q 6.1.4	**Does the use of recombinant growth hormone improve nutritional status in pre-pubertal people with CF?**
R 6.1.4	GRADE C. There is some evidence to suggest that growth hormone may improve height, weight and lean tissue mass for pre-pubertal people with CF. Routine use of growth hormone to improve nutritional status in people with CF is not recommended. [12]
PP 6.1.3 and PP 6.1.4	The decision to commence an appetite stimulant should made as an interdisciplinary team and in consultation with the individual with CF and their family or carers, following evaluation of potential benefits and risks in the individual with CF. The most commonly used appetite stimulants in CF are megesterol acetate and cyproheptadine (periactin). • They may improve weight and appetite but evidence is inconclusive. • Some concerns regarding side effects and therefore safety with longer term use. Growth hormone may improve height, weight and lean tissue mass for pre-pubertal individuals with CF, however, longer term randomized controlled trials are required. • Until more studies are done looking at the longer term use of growth hormone, it is not recommended for routine use CF Prior to commencing a trial of appetite stimulants in CF, issues to explore include: • Identification of other factors that may be contributing to a poor appetite and subsequently poor weight gain or growth and where possible, treat the underlying cause first • Potential side effects of each appetite stimulant. • The role of other factors which may impact oral intake including (but not limited to) reflux, intestinal dysmotility and early satiety.

Oral Nutritional Supplements	
Q 6.1.5	**Is there any rationale for the use of commercial oral nutritional supplements in addition to food and mealtime strategies to improve nutritional intake, weight or pulmonary function in CF?**
R 6.1.5	GRADE B. Consider the use of oral nutrition supplements on an individual basis. There is no clear evidence that their routine use in addition to food and behavioural modification strategies will result in improvements to nutritional intake, weight or pulmonary function in CF. [13-19]
PP 6.1.5	Where possible, avoid using oral supplements as a meal substitution • Oral supplements should complement usual intake • Best taken after a meal or as a snack • A maximum of three oral supplements daily is often recommended to avoid a reduction in appetite around mealtimes. • Particularly important for the paediatric population where normalised eating is still developing. Regularly review oral supplement tolerance, adherence and nutritional status response. The most commonly used oral supplements in CF are dairy based and usually 1-1.5kcal/ml. Evaluate individual cost versus benefit because oral supplements can be a financial burden because funding for nutrition support varies across the health systems in Australia and New Zealand.
Enteral Feeding	
Q 6.1.6	**Should enteral feeding be considered to improve nutrition outcomes for people with CF?**
R 6.1.6	GRADE B. Consider enteral feeding as a means of improving markers of nutritional status (including weight, BMI and BMI z-score) in children and adults with CF who have been assessed as being undernourished. [20-29]
Q 6.1.7	**Should enteral feeding be considered to improve pulmonary status in people with CF?**
R 6.1.7	GRADE C. Practitioners should refrain from commencing supplementary enteral feeding for the sole purpose of improving or stabilizing pulmonary outcomes. [20-26,28]
PP 6.1.6 and 6.1.7	The decision to commence either short or long term enteral nutrition support should be made by an interdisciplinary team and in consultation with the individual and their family, including discussion of risks and benefits. • Benefits on nutrition outcomes, particularly weight and BMI are well documented • There is no conclusive evidence to support beneficial effects on pulmonary function The decision can be emotionally challenging for some people with CF. Where possible, appropriate psychosocial support should be provided and the individual's decision should be respected. An anaesthetist should be consulted prior to surgical or endoscopic gastrostomy tube insertion in people with moderate to severe CF lung disease.
Q 6.1.8	**When should enteral feeding be introduced for people with CF?**
R 6.1.8	UNGRADED. There is insufficient evidence to make a recommendation regarding when to introduce enteral nutrition in CF. Evaluate appropriate timing on an individual basis.
PP 6.1.8	No evidence to support best timing for enteral nutrition support in CF. The following considerations should be noted in regards to timing of enteral nutrition: • The person is unable to meet nutritional requirements via oral intake alone • Conduct Interdisciplinary review with investigation of reasons for any decline in nutrition status and interventions commenced as appropriate • Explore the role for behavioural modification strategies (In the paediatric population) • Whilst many patients will have had a trial of oral nutritional supplements (ONS) prior to the need for enteral nutrition being assessed, there is no evidence that favours assessing the impact of ONS first, over proceeding to enteral nutrition. Evaluate whether to trial ONS prior to considering enteral nutrition on an individual basis • Enteral nutrition should be commenced prior to the onset of significant disease progression and FEV_1 decline for more favourable nutritional outcomes

Q 6.1.9	**What is the ideal enteral feeding regimen for people with CF?**
R 6.1.9	UNGRADED. There is insufficient literature to suggest the ideal enteral formula or regimen in the CF population. Select enteral formulas and devise enteral feeding regimens on an individual basis.
PP 6.1.9	Enteral feed regimens should be devised on an individual basis The following considerations should be assessed in relation to the individual: • Caloric targets should be calculated by the specialist dietitian. • Overnight continuous feeds are usually recommended to preserve appetite and oral intake during the day, though supplementary bolus feeds may also be useful for some people. • Feed composition • The choice between polymeric, semi-elemental and elemental feeds should be made on an individual basis. • Many people with CF will tolerate polymeric feeds well and more specialised formulas are not usually required. • Choose energy dense feeds i.e. 1.5-2kcal/ml where possible • Evaluate individual cost/financial burden versus benefit because funding for enteral nutrition varies across the health systems in Australia and New Zealand. • Feed tolerance should be reviewed regularly • Co-morbidities such as reflux may play a role in feed regimens and enzyme dosing strategies (Chapter 10). • Feeding route • Nasogastric feeding is usually recommended when feeds are required for < 3 months. • Gastrostomy insertion should be considered when feeds are required for > 3 months. For supplementary feeding, aim to meet 30-60% of the individual's calculated energy requirements, or to meet a specifically calculated energy deficit in the diet.
Q 6.1.10	**What are the risks associated with enteral feeding in CF compared to the general population?**
R 6.1.10	GRADE C. There is no evidence that people with CF are at increased risk of major complications and mortality as a result of enteral feeding. Manage minor side effects of enteral feeds, including stoma site issues and GOR, as for the general population. [20-27,29]

PP 6.1.10	Enteral feeds are considered safe for the CF population. However, as with any intervention, potential risk factors should be evaluated and investigated prior to feed commencement.
	
	Safety considerations around enteral feeding include, but are not limited to the following:
	• Nasogastric tubes
	• Insertion may be difficult and uncomfortable for people with nasal polyps
	• Tubes may be dislodged with significant coughing and/or vomiting
	• Gastrostomy tubes
	  ○ Aim to optimise pulmonary to health prior to placement of gastrostomy tube
	  ○ Plan for postoperative pain management with the goal of initiating airway clearance within 24hrs
	  ○ Gastrostomy site, itchiness, redness and infection are common. Regular stoma monitoring is recommended.
	• GOR
	  ○ Positioning: ensure the person is elevated to a 30-45% angle during feeding, reducing feed rate and post pyloric feeding may be of assistance
	• Bloating or nausea during enteral feeds may benefit from the use of prokinetic or antiemetic agents prior to feeding.
	• Potential risk of hyperglycaemia or CF-related diabetes. Blood glucose monitoring is indicated prior to, mid-way through and at the end of feeding.
	
	Dietetic department protocols should guide the use of gastrostomy tube and care education prior to discharge home with a feeding tube.

Chapter 7 **Macronutrients**	
Energy	
Q 7.1.1	**Are energy requirements increased in the CF population compared to the general population?**
R 7.1.1	GRADE D. Limited evidence to guide determination of energy requirements for people with CF of all ages. Until further evidence is available, health professionals should be guided by the consensus recommendation of 110-200% of the general population energy target. Use clinical reasoning and an individualised approach to setting energy targets. [30-42]
PP 7.1.1	Energy requirements are likely to be elevated for people with CF. Aim for 110-200% of the recommended daily energy intake for age and gender when setting energy targets for the CF population. Take into account the following when setting individualised energy targets for people with CF: • Nutritional status • Dietary intake • Growth pattern – aiming to achieve normal growth (avoid both undernutrition and overweight/obesity) • Clinical status (including pulmonary function) • Pancreatic function • Physical activity • Any additional requirements for weight gain/growth and nutritional repletion • Pregnancy and lactation • Transplantation
Protein	
Q 7.1.2	**Are protein requirements increased in the CF population compared to the general population?**
R 7.1.2	UNGRADED. Insufficient evidence to make a recommendation about protein requirements
PP 7.1.2	Aim for 15-20% energy from protein. Take into account the following when setting individualised protein targets for people with CF: • Protein intake generally increases as energy intake increases A mixed high energy diet should provide adequate protein for people with CF Vegans, vegetarians, fussy/restrictive eaters, people with allergies i.e. cow's milk protein allergy and the obese CF population on an energy restricted diet, will require specific dietary advice regarding protein intake Further research is needed into the impact of protein quality on health outcomes in CF. Protein requirements may be elevated with malabsorption and catabolism. It is particularly important to consider the adequacy of protein intake for people with CF who have signs/ symptoms of malabsorption, are unwell e.g. with a respiratory exacerbation or poorly controlled diabetes. • Upper Limit for protein: The NHMRC recommends an upper limit for protein of 25% of energy intake for the general population,[43] however there is no evidence to guide a CF-specific upper limit. Evaluate individual dietary practices contributing to protein intake when intake is above 25% of energy intake; to identify if the high protein intake is contributing to a specific nutritional goal, or if other sources of energy and nutrients can be substituted without compromise to overall nutritional intake and status.
Fat	
Q 7.1.3	**What is the evidence to support the routine recommendation of a high fat diet for people with CF?**
R 7.1.3	GRADE D. There were no new studies included in this systematic literature review (2002-2016) to make changes to the existing recommendation for fat intake in CF from the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*[1]. Continue to recommend an unrestricted diet that contains adequate fat to meet energy requirements. Target an intake of 100g/day if over five years of age based on the premise that a diet high in fat is less bulky and energy targets are more achievable than a diet that is low in fat.

PP 7.1.3	Providing the person is not overweight or at risk of overweight/obesity, avoid restricting fat intake in people with CF
	• Aim for 100g/day of fat for people with CF aged >5 years
	Take into account the following in setting individualised fat targets for people with CF:
	• Source and quality of fat i.e. polyunsaturated and monounsaturated versus saturated fat
	  ○ Potential implications of a high saturated fat diet on cardiovascular health
	  ○ Potential benefits of long chain polyunsaturated fatty acids on inflammation
	• Macronutrient distribution
	  ○ Initially aim for 20-30% energy from fat, according to the recommendations for the general population
	  ○ Up to 35-40% energy from fat is considered acceptable for the paediatric CF population and for those requiring a high energy density diet (e.g. for nutritional repletion).

Q 7.1.4	**What are the recommendations for fibre in people with CF?**
R 7.1.4	UNGRADED. Insufficient evidence to make a recommendation about fibre intakes.
PP 7.1.4	Aim for a moderate fibre intake in line with the general population recommendations of 14-30g dietary fibre per day. Refer to the Nutrient Reference Values for Australia and New Zealand webpage, https://www.nrv.gov.au/nutrients/dietary-fibre for specific age and gender recommendations.
Essential Fatty Acids	
Q 7.2. 1	**Does dietary supplementation with omega-3 essential fatty acids improve health outcomes in people with CF?**
R 7.2.1	GRADE C. Dietary supplementation with omega-3 fatty acids may improve health outcomes for people with CF, however, the evidence is insufficient to recommend routine use of omega-3 supplementation. [44-46]
PP 7.2.1	People with CF may be at risk of EFA deficiency • The prevalence of EFA deficiency in CF is unknown **Omega-6 fatty acids** - Includes linoleic acid (LA), a precursor of arachidonic acid (AA) • LA occurs in seed oils (sunflower, safflower and corn) • AA occurs in meat, poultry and eggs • Can exert a pro-inflammatory effect **Omega-3 fatty acids** – Includes alpha linolenic acid (ALA), a precursor of the long-chain PUFAs (Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA)) • ALA occurs in legumes, canola oils, margarine, linseed oils and nuts (walnuts) • Long-chain omega-3 PUFAs occur in fish oils • Known for their anti-inflammatory properties **Source of supplementation** • Insufficient evidence to suggest that any type or combination of omega-3 EFA (dietary or commercial) is superior. Take into account the following prior to recommending omega-3 supplements to people with CF: • Safety – intakes above 5000mg/d have been associated with an increase in oxidative stress and gastrointestinal discomfort • Efficacy – long term efficacy of omega-3 supplementation in CF is unknown • Cost of commercial omega-3 supplements • Impact on burden of treatment and adherence • May be better tolerated with meals (and PERT)

Chapter 8 **Fat Soluble Vitamins**	
Vitamin A	
Q 8.1.1	**How should vitamin A be assessed for people with CF?**
R 8.1.1	UNGRADED. There is insufficient evidence to make a CF-specific recommendation about assessing vitamin A status. In the absence of evidence health professionals should continue to use serum retinol when assessing vitamin A status. Explore the addition of tests to assist with the interpretation of vitamin A status including, zinc, retinol binding protein (RBP), an inflammatory marker and retinol : RBP molar ratio, though there is limited evidence for their use in CF. Serum retinyl esters may be tested for the assessment of vitamin A toxicity. There is no evidence to recommend the routine assessment of β-carotene levels.
PP 8.1.1	Serum retinol is the most common and readily available measure of vitamin A deficiency status, however there is significant variability in what is used to define deficiency, adequacy and excess. • Interpret results using reference ranges provided by the laboratory doing the test. • Where possible measure levels when clinically stable. Acute illness may result in decreased serum retinol. • Ideally measure when fasting. Non-fasting levels may reflect recent intake of vitamin A. If low serum retinol levels despite recommended supplementation consider: • Adherence with recommended vitamin supplementation • Whether supplements are being taken with PERT and fat containing meal Measure the following to assist in the interpretation of serum retinol; ○ A marker of inflammatory status such as CRP ○ Zinc ○ Retinol binding protein ○ Other fat soluble vitamin levels • Acute illness / increased inflammation will result in increased inflammatory markers and decreased levels of serum retinol, zinc and RBP. • If retinol, zinc and RBP are all low in the setting of raised inflammatory markers, then results most likely reflective of acute illness not vitamin status. Recommend re-assess levels when patient clinically stable. • If serum retinol is still low despite normal inflammatory markers, serum zinc and RBP, measure the molar ratio of RBP : retinol. This will assist in the interpretation of retinol levels and the adequacy or excess of supplementation. A ratio <0.8 suggests deficiency of vitamin A. Supplement vitamin A as per recommendation 8.1.3 and practice point 8.1.3. • If serum zinc is low or zinc status assessed as likely deficient, supplementation of zinc may be beneficial. Note that serum zinc is not a sensitive or specific test of zinc status and zinc may be normal even with subclinical zinc deficiency (Chapter 9). • If RBP is low in the setting of normal inflammatory markers, be cautious with high dose supplementation, particularly in those with CF-related liver disease. Gastroenterologist advice is recommended (Chapter 11). Enquire about symptoms such as poor night time vision if deficiency is suspected. Poor night vision will manifest prior to xeropthalmia. If high serum retinol; • Consider if fasting levels. High levels may reflect recent intake of vitamin A. • Assess Retinol : RBP ratio. A ratio >1.0 may indicate excess intake and toxicity. If the person with CF is on high dose supplementation and at risk of vitamin A toxicity; • Assess Retinol : RBP ratio. A ratio >1.0 may indicate toxicity Measure serum retinyl esters as a function of total serum retinol. Serum retinyl esters >10% of the total vitamin A pool are usually considered abnormal.

Q 8.1.2	**What is the role for routine supplementation of vitamin A in people with CF and pancreatic insufficiency?**
R 8.1.2	GRADE D. Routine supplementation of vitamin A in all people with CF and PI is recommended (table 8e) (unchanged from the *'2006 Australasian Clinical Practice Guidelines for Nutrition in CF')*[1]. There is inadequate evidence at this time for the routine adjunctive supplementation of β-carotene as an antioxidant. [47-61]
PP 8.1.2	For people who are pancreatic insufficient fat soluble vitamin supplementation should be commenced at diagnosis and, if indicated, continued throughout life. Aim to achieve serum retinol levels within the normal population reference ranges. *'2006 Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis'*[1]*:* • Infants: 1500-2000 IU vitamin A /day • Young children: 1500-5000IU vitamin A /day • Older children, adolescents and adults: 2500-5000IU vitamin A / day Evaluate the need for supplementation on an individual basis for the pancreatic sufficient population.
Q 8.1.3	**What vitamin A supplementation dose should be prescribed to treat vitamin A deficiency in people with CF?**
R 8.1.3	GRADE D. In the absence of quality evidence for supplementation to treat subclinical vitamin A deficiency in people with CF, it is recommended to follow the doses recommended in the *'2006 Australasian Clinical Practice Guidelines for Nutrition in CF*[1] as outlined in Table 8e (Chapter 8). There is no evidence specific to people with CF for supplementation to treat severe deficiency. Assess supplementation on an individual basis with interdisciplinary input and referral to relevant disciplines outside of CF as appropriate.
PP 8.1.3	• In cases of subclinical deficiency supplement as per table 8e (Chapter 8) above guidelines aiming to achieve serum retinol levels within the normal population reference ranges. • If RBP : retinol ratio indicates deficiency i.e. <0.8, increase supplementation to upper limits of recommended supplementation e.g. adults to 10 000IU. • Low RBP may occur in those with severe liver disease. Be cautious with high dose supplementation in these circumstances. Recommend consultation by gastroenterologist. See chapter 11 for supplementation recommendations in CF-related liver disease. • For vitamin A deficiency refractory to upper level of recommended supplementation, think about an empiric trial of zinc supplementation. See chapter 9 • Severe vitamin A deficiency with overt symptoms will require high dose supplementation (>10,000IU). An individualised approach with interdisciplinary input including CF physician, dietitian and appropriate other health professionals such as gastroenterologist is recommended.
Q 8.1.4	**What is the safe upper limit for vitamin A supplementation in people with CF?**
R 8.1.4	UNGRADED. There is insufficient evidence available regarding the safe upper limit for vitamin A supplementation in CF. In the absence of evidence specific to CF, health professionals should be guided by recommendations for the general population.

PP 8.1.4	Be guided by upper limits for the general population. Note upper limits are for preformed vitamin A as retinol. Australian and New Zealand Nutrient Reference Values (2006) [43]; • Infants: 2000 IU vitamin A • Young children: 2000 – 3000 IU vitamin A • Older children: 5667 IU vitamin A • Adolescents: 9333 IU vitamin A • Adults: 10 000 IU vitamin A Supplementation for severe vitamin A deficiency may require doses greater than the above recommended upper limits. Supplementation doses in excess of these upper limits should be advised with caution and only following a thorough interdisciplinary assessment of potential risks and benefits. Referral to a gastroenterologist with CF experience is recommended. • Where vitamin A toxicity is a concern, consider additional supplementation in the form of β-carotene, as excessive ingestion of this form is generally considered safe. • In the absence of an available β-carotene supplement, a regular multivitamin with greater proportion of vitamin A as β-carotene may be considered. However additional supplementation of other fat soluble vitamins may be required, with an increase cost and burden to person with CF. Monitor serum retinol, RBP, retinol : RBP ratio and if available serum retinyl esters for those on high dose supplements.
Q 8.1.5	**How often should vitamin A levels be measured in people with CF?**
R 8.1.5	UNGRADED. There is insufficient evidence available to recommend specific monitoring and evaluation protocols for vitamin A levels in CF. Health professionals should continue to follow recommendations in the '*2006 Australasian Clinical Practice Guidelines for Nutrition in* CF', to assess annually and monitor more frequently in those at high risk of deficiency or toxicity[1].
PP 8.1.5	Monitor vitamin A status annually. More frequent monitoring (e.g. 3-6 monthly) is suggested in the following scenarios: • After changing supplementation doses, especially after high dose supplementation • For people with CF-related liver disease or history of intestinal resection or malabsorption • In people with poor adherence to PERT and fat soluble vitamin supplementation • After changes to treatment for malabsorption where a change in the level of fat absorption has occurred • On some drugs such as acne medications e.g. Roaccutane®
Vitamin D	
Q 8.2.1	**Is vitamin D status associated with measures of respiratory health (lung function, pulmonary exacerbations, markers of inflammation) in people with CF?**
R 8.2.1	Grade D. At this stage there is insufficient evidence that vitamin D status is associated with measures of respiratory health in people with CF. [62-68]
PP 8.2.1	There is no evidence to support a causal role between vitamin D and respiratory health, however it is reasonable to assume that individuals with severe lung disease may be more likely to be vitamin D deficient due to spending more time indoors.
Q 8.2.2	**Is there an ideal serum 25-hydroxyvitamin D level to aim for in people with CF?**
R 8.2.2	UNGRADED. Insufficient evidence specific to CF for the ideal serum 25-hydroxyvitamin D level. It is suggested that the general Australian and New Zealand goal of ≥50 nmol/L[69] be used with a caveat for the time of year at which testing occurs.
PP 8.2.2	It is suggested that the general Australasian goal of ≥50 nmol/L serum 25(OH)D be used if measuring vitamin D at the end of winter or in early spring[69]. If testing at other times of year, aim for a level 10-20nmol/L higher (i.e. ≥60-70nmol/L).
Q8.2.3	**Is the time of year, specifically the season, important when measuring and interpreting an individual's serum vitamin D level?**

R8.2.3	GRADE C. Aim to measure serum vitamin D at the end of the winter months and adjust supplementation accordingly. If not feasible, take into account the season of assessment when interpreting results and prescribing supplementation. [51,64,65,70-74]

PP8.2.3	• Aim to measure serum vitamin D at the end of winter/early spring
	• Take into account the following when interpreting results:
	  • ≥50nmol/L = adequate at the end of winter or in early spring
	  • ≥60-70nmol/L = adequate at other times of the year
	• Specific considerations for the Australian and NZ context:
	  • Seasonal variations may differ according to geographic location
	People from far north of Australia who spend time outdoors during the winter months, may not see as much seasonal variation in serum vitamin D levels

Q8.2.4	**Should supplemental vitamin D be given to people with pancreatic sufficient cystic fibrosis as part of routine care?**
R8.2.4	GRADE C. There is inconsistent evidence to support routine vitamin D supplementation for all people with CF, regardless of pancreatic status. It is recommended that all people with CF undergo annual serum vitamin D testing and be supplemented accordingly. [51,64,65,71,72,74-76]
PP 8.2.4	Consider all individuals, including those with pancreatic sufficiency at risk of vitamin D deficiency and screen annually. Supplement as required.
Q 8.2.5	**What doses of vitamin D are needed to prevent deficiency in people with CF?**
R 8.2.5	UNGRADED. There is insufficient evidence available to recommend evidence-based routine supplementation doses for people with CF
PP 8.2.5	Base routine supplementation of vitamin D on the US and European consensus documents[77,78]: ○ Infants = 400-1000 IU ○ Young children = 800-2000 IU ○ Older children, adolescents and adults = 800-4000 IU Additional points: • Take into account medication adherence and cost when prescribing supplementation • Ergocalciferol and cholecalciferol are the two forms of vitamin D available • Cholecalciferol should be used as it most effective in increasing serum 25OHD levels. • Cholecalciferol is the major form of supplemental vitamin D currently available in Australia and New Zealand.
Q 8.2.6	**What doses of vitamin D are needed to correct deficiency in people with CF?**
R 8.2.6	GRADE C. There is a lack of evidence on conventional, daily doses of vitamin D needed to correct vitamin D deficiency. ○ Health professionals should be guided by consensus based guidelines[77,78] There is some evidence to support the use of high dose cholecalciferol ("STOSS therapy") in CF. Use with caution due to risk of toxicity in those who are unable to convert excess cholecalciferol to its inactive form. [79,80]
PP 8.2.6	Base supplementation of vitamin D to correct deficiency on the US and European consensus documents[77,78]: • Infants = 400-2000 IU • Young children = 1000-5000 IU • Older children, adolescents and adults= 1000-10 000 IU • Before escalating treatment of vitamin D deficiency, check adherence to PERT and prescribed vitamin supplementation. • Use of high dose vitamin D supplementation (STOSS) should be carefully evaluated and done in conjunction with an endocrinologist with experience in CF. Some people are unable to convert excess cholecalciferol to its inactive form and are therefore at increased risk of toxicity. • Refer to an endocrinologist if people are unresponsive to maximal treatment doses.

Vitamin E	
Q 8.3.1	**How should vitamin E status be assessed for people with CF?**
R 8.3.1	UNGRADED. There is insufficient evidence to make a CF-specific recommendation about assessing vitamin E status. In the absence of evidence health professionals should continue to use serum α-tocopherol when assessing vitamin E status. Lipid adjustment may provide a more accurate assessment of vitamin E status and its use may be explored where available.
PP 8.3.1	Serum or plasma levels of α-tocopherol are the most common measure used to assess vitamin E status. However there is significant variability in what is used to define deficiency, adequacy and excess. • Interpret results using reference ranges provided by the laboratory doing the test. Measurement of α-tocopherol to total lipid ratio will aid in the interpretation of serum vitamin E status in the following situations: • Abnormal serum α-tocopherol levels • Abnormal lipid levels (common in CF and liver disease) o Normal ratio in children = 0.6mg/g o Normal ratio in adults = > 0.8mg/g When not available, the α-tocopherol to cholesterol ratio can be used in place of total lipid ratio although; o Overall a less sensitive and specific test o Aim for a ratio >5.4mg/g in CF o Where possible measure fasting levels of total lipid ratios. There is no evidence for the assessment of other tocopherols including γ-tocopherol in CF
Q 8.3.2	**What is the role for supplementation of vitamin E in people with CF?**
R 8.3.2	GRADE C. Routinely supplement vitamin E in people with CF who are pancreatic insufficient. For pancreatic sufficient individuals commence supplementation on an individual basis. There is inadequate evidence to establish recommendations for supplement dose specifically for CF. Overall the evidence is insufficient to recommend change from current practice as per the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*' (Table 8j) (Chapter 8).[1] 47-54,81-86
PP 8.3.2	Routine supplementation of vitamin E is recommended for all pancreatic insufficient people with CF. Aim to achieve the normal population reference ranges. At this time, continue to follow the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*' when supplementing vitamin E in CF[1]: o Infants: 40 - 80IU/day o Children 1 to 3 years: 50 - 150IU/day o Children 4 to 7 years: 150 - 300IU/day o Children > 8 years & Adults: 300 - 500IU/day Consider supplementation on an individual basis for the pancreatic sufficient population. Higher supplementation doses may be required if significantly increased dietary and/or supplemental polyunsaturated fatty intakes. • If ongoing deficiency despite recommended levels of supplementation, consider adherence to prescribed supplement and PERT before increasing the dose further. • Water-miscible vitamin E preparations are generally more bioavailable than fat soluble preparations.

Q 8.3.3	**What is the safe upper limit for vitamin E supplementation in people with CF?**
R 8.3.3	UNGRADED. There is insufficient evidence available regarding the safe upper limit for vitamin E supplementation in CF. Health professionals should be guided by the upper limit of the age-specific supplementation ranges recommended in the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*' for routine supplementation of vitamin E (table 8j)[1]. Make a thorough assessment of risks and benefits before considering higher supplement doses as required to correct deficiency states, and closely monitor the response to supplementation.
PP 8.3.3	A safe upper limit has not yet been determined for vitamin E supplementation in CF. No evidence of vitamin E toxicity in CF. Supplementation above the upper recommended dose should only be considered following thorough dietary and clinical assessment and based on serum levels.
Q 8.3.4	**How often should vitamin E levels be measured in people with CF?**
R 8.3.4	UNGRADED**.** Insufficient evidence to make a recommendation. Health professionals should continue to follow recommendations in the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*', to assess annually and to monitor more frequently in those at high risk of deficiency or toxicity[1].
PP 8.3.4	Assess vitamin E status annually. Monitor more frequently in the following groups: • Infants: 2 months post first commencing supplementation [87] • After changing supplementation doses i.e. 3-6 months post changes • After changes to treatment for malabsorption where a change in the level of fat absorption has occurred. • People with CF-related liver disease or history of intestinal resection or malabsorption • People with poor adherence to PERT and fat soluble vitamin supplementation
Vitamin K	
Q 8.4.1	**How should vitamin K status be assessed for people with CF?**
R 8.4.1	UNGRADED. There is insufficient evidence to make a recommendation about methods for assessing vitamin K status. At this time, it is recommended that health professionals assess vitamin K status using the best readily available biochemical measure together with a thorough diet and clinical assessment.
PP 8.4.1	• There is no readily available direct measure of vitamin K status (sufficiency or deficiency). • Serum vitamin K is unreliable and should not be used to assess vitamin K status in CF. • PIVKA-II (protein induced vitamin K absence-II) and uc-OC (undercarboxylated osteocalcin) are considered the most accurate measures of vitamin K status. o Not readily available in clinical practice in Australia and New Zealand • Prothrombin Time (PT) is a measure of coagulation and is often used as a more readily available surrogate measure of vitamin K status. Consider the following prior to use: o Insensitive and non-specific o Marker of advanced vitamin K deficiency. o Not recommended in infants, other than those with CF-related liver disease as it requires large amount of blood for collection o Ideally assess biochemical status using a more accurate measure such as PIVKA-II, however where not available, use surrogate measure of PT.
Q 8.4.2	**Should vitamin K supplementation be recommended for all people with CF and pancreatic insufficiency?**
R 8.4.2	GRADE C. Routinely supplement vitamin K in all people with CF and pancreatic insufficiency as outlined in table 8l (Chapter 8). In practice supplementing at these doses will require an increase in vitamin K supplementation doses that are routinely provided and currently available in Australia and NZ. There is insufficient high quality evidence available to recommend an optimal dose. [85,88-95]

PP 8.4.2	Vitamin K supplementation is recommended for all pancreatic insufficient people with CF. At this time, it is recommended to follow the most recently released international guidelines for vitamin K supplementation dosing in CF. • *ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children and adults with cystic fibrosis*[78] ○ Infants: 300 - 1000µg ○ Children & Adults: 1000 – 10 000 µg Higher doses may be required for those with CF-related liver disease, intestinal resection or when on longer term antibiotic or steroid regimens. Daily administration of vitamin K is preferred due to the body's low storage capacity. Vitamin K preparations in Australia and New Zealand all contain vitamin K1 (phytomenadione), however in amounts well below recommended supplementation doses. Additional supplementation of vitamin K may be required particularly for those considered at high risk of deficiency and/or with bone disease, however, evaluate the availability, cost and treatment burden for people with CF.
Q 8.4.3	**How often should vitamin K levels be measured in people with CF?**
R 8.4.3	UNGRADED. Insufficient evidence to make a recommendation. Aim to assess vitamin K status at diagnosis and annually in all people with CF.
PP 8.4.3	Aim to assess vitamin K status annually. • Additional screening for vitamin K deficiency should be considered for newly diagnosed patients and those with haemoptysis/haematemesis, CF-related liver disease or recent intestinal resection. Vitamin K status should ideally be re-checked 3 months after any change to vitamin K supplementation or treatment for malabsorption.

Chapter 9 **Minerals**	
Iron	
Q 9.1.1	**How should iron status be assessed in people with CF?**
R 9.1.1	GRADE C. The level of evidence to guide practice for assessing iron status in CF is insufficient. Further research or expert consensus is required. Until further evidence is available, it is suggested that iron status in CF be assessed as per guidelines for the general population. [96,97]
Q 9.1.2	**How should iron deficiency be treated in people with CF?**
R 9.1.2	UNGRADED. Insufficient evidence to make a recommendation
Q 9.1.3	**Is iron supplementation contraindicated for people with CF who are chronically colonised with pseudomonas aeruginosa (PA)?**
R 9.1.3	GRADE D. There is insufficient evidence from clinical trials to suggest that iron supplementation is contraindicated in adults and children with CF who are chronically colonised with *Pseudomonas aeruginosa*. When indicated, an iron supplement should be prescribed for adults and children with CF who are chronically colonised with *Pseudomonas aeruginosa*. [98]
PP 9.1.1, 9.1.2 and 9.1.3	Increased risk of iron deficiency in CF due to chronic inflammation, inadequate dietary intake, gastrointestinal comorbidities and haemoptysis. Iron studies are difficult to interpret in CF due to chronic inflammation. Aim to assess iron status during clinical stability. **Interpretation of biochemical markers in CF -** Serum ferritin is an acute phase protein (rises during periods of inflammation) and may be unreliable. Inflammatory markers, including C-reactive protein (CRP) should be taken into consideration. • Serum transferrin receptor (sTfr) is not readily available but should be considered as it is not affected by inflammation. A raised sTfR may be a useful indicator of functional iron deficiency in CF.

PP 9.1.1, 9.1.2 and 9.1.3	**Absolute iron deficiency -** Iron stores are depleted, as indicated by serum ferritin (low), serum iron (low), transferrin (high), transferrin saturation (low), sTfR (high), CRP (normal) • Oral iron supplementation is recommended **Functional iron deficiency** - Iron stores are normal-high but not available at the site of erythroblast production. Serum ferritin (low – normal), serum iron (low), transferrin (normal-high), transferrin saturation (low), sTfR (high), CRP (high) • Oral iron supplementation may be required **Dietary considerations** Increasing dietary iron intake is often inadequate in the treatment of iron deficiency in CF. Iron is available in food as haem iron (more bioavailable) and non-haem iron (less bioavailable). • Meat, seafood and poultry are good sources of haem iron. • Plant-based foods (wholegrain cereal and green leafy vegetables) and iron-fortified foods (infant rice-cereal) are good sources non-haem iron. • Foods high in vitamin C improve the absorption of iron. • Foods high in calcium, phytates (legumes, rice and other grains) and tannins (tea) can inhibit the absorption of iron. **Oral iron supplement considerations** Prescribe an iron supplement, in addition to dietary change, for 2-3 months to treat diagnosed iron deficiency. Suggested treatment doses: • Children: 3-6mg/kg/d elemental iron for 2-3 months after serum Hb normalises • Adolescents & adults: 100-200mg elemental iron daily for 3-6 months after Hb normalises • Gastrointestinal complaints (including constipation and epigastric pain) are common side effects of oral iron supplements. Multivitamins are not recommended in the treatment of iron deficiency. Concerns regarding potential drug-nutrient interactions should be discussed with the CF pharmacist. Iron supplementation is not contraindicated for people with CF with chronic Pseudomonas aeruginosa infection. **Intravenous iron supplementation** Iron (ferric carboxymaltose) 500mg/10ml injection is associated with fewer adverse events than other IV iron supplements. It is also available on the pharmaceutical benefits scheme (PBS) in Australia and via PHARMAC in New Zealand (District Health Board hospitals only)
Magneisum	
Q 9.2.1	**Does supplementing magnesium above the RDI improve nutrition and/or respiratory outcomes in people with CF?**
R 9.2.1	GRADE D. There is insufficient evidence to support that routine magnesium supplementation above the RDI improves health outcomes in people with CF. Explore the use of oral magnesium supplementation only when dietary intake is unable to meet the RDI. [99]
PP 9.2.1	Encourage people with CF to achieve adequate consumption of magnesium as part of a varied diet. • Foods high in magnesium include green leafy vegetables, unrefined cereals, legumes, nuts & shellfish • Magnesium deficiency is likely to co-exist with other micronutrient deficiencies. A nutrition review should therefore consider overall micronutrient adequacy. Oral magnesium supplementation is considered safe and cost-effective High dose magnesium supplementation may result in gastrointestinal side effects, especially diarrhoea. This is most commonly seen in patients on higher dose magnesium supplements after lung transplantation.
Calcium	
No PICO questions were formulated for section 9.3. Refer to Chapter 9, section 9.3 Calcium for narrative text.	

Sodium	
Q 9.4.1	**How do environmental factors and exercise impact on sodium requirements for people with CF compared to those without CF?**
R 9.4.1	GRADE C. Climate (heat and humidity) is thought to have an impact on salt requirements in CF. There is also some evidence to support an altered thirst drive for people with CF. However, at this time, there is insufficient evidence available to conclude how environmental factors and exercise impact on sodium requirements for the wider CF population. [100-102]
PP 9.4.1	Take into account the following when evaluating sodium requirements: • Infants & people with CF exposed to hot / humid environments or illness are at high risk of sodium depletion & hyponatraemia. • Signs & symptoms of sodium depletion include nausea, vomiting, muscle cramps, deposition of salt crystals on the skin, fatigue, poor growth (especially in infants) and/ or hyponatraemia • Sweat sodium losses vary amongst individuals (with and without CF) • Dietary intake, sweat rate, hydration and heat acclimation can impact on sodium losses. • Sweat rates/sodium losses are elevated and thirst drive potentially diminished for people with CF in hot / humid conditions and during exercise. Dehydration/hyponatraemia is a risk under these conditions.
Q 9.4.2	**What is the recommended daily sodium requirement for people with CF compared to those without CF?**
R 9.4.2	GRADE D. There is a lack of research available to guide sodium requirements for people with CF. As a result, recommendations vary in international consensus and review documents. Recommendations for daily sodium requirements in CF are: • Infants - 500-1000mg • Children - 1000-4000mg • Adolescents and adults - 6000mg (unchanged from the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*[1])
PP 9.4.2	• Clinicians should continue to use nation-specific guideline/consensus documents (including the '*2006 Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis*' in addition to a thorough nutrition assessment and clinical judgment as a guide when recommending sodium supplementation to people with CF [1]. • Serum sodium is not a sensitive marker for salt depletion in CF. • Undertake a spot urine sodium analysis if sodium depletion is suspected or supplementation significantly changes. • Clinicians should be guided by local climate-based recommendations and clinical judgment when individually tailoring sodium supplementation to people with CF.
Zinc	
Q 9.5.1	**How should Zinc status be assessed for people with CF?**
R 9.5.1	Grade D. The level of evidence to guide practice for assessing zinc status in CF is insufficient. Further research or expert consensus is required. [103]

PP 9.5.1	Assess zinc status and monitor empiric trials of zinc supplementation using a combination of dietary, biochemical and clinical/functional indicators.
	Serum/Plasma Zinc
	• Measure using the local laboratory reference ranges.
	• Analyse levels in the context of dietary and clinical information. Consider;
	  ○ Zinc is an insensitive marker of deficiency however may be helpful diagnostically in severe zinc deficiency
	  ○ Levels are best measured when person with CF is clinically stable. Where acute phase response and inflammation is suspected, check CPR.
	  ○ There is high individual biological variation in zinc levels
	  ○ There is diurnal variation in zinc levels and levels may reflect recent dietary intake. Recommend where possible to measure fasting levels.
	Clinical Indicators
	• Marginal zinc deficiency may be diagnosed in some patients via a positive response to zinc supplementation e.g. improved growth.
	• Evaluate differential diagnoses as other conditions may present with similar signs and symptoms of zinc deficiency.
	Diet
	• Attention should be given to those at high risk of inadequate zinc intakes/absorption;
	  ○ Strict vegetarian diets with high intake of phytates
	  ○ Infants older than 6 months exclusively breastfed or consuming limited high bioavailable zinc foods such as fortified cereals or meat
	  ○ High iron supplementation
	Assess adequacy of protein and essential fatty acids because deficiency may manifest similarly to zinc deficiency.

Q 9.5.2	**What are the recommendations for zinc supplementation in people with CF?**
R 9.5.2	Grade D. There is insufficient evidence to make recommendations for routine supplementation or supplementation for suspected zinc deficiency in CF. Until further evidence is available, it is suggested that zinc supplementation be guided by recommendations in CF consensus guidelines. As per the 2016 ESPEN-ESPGHAN-ECFS CF nutrition guidelines[78], CF people at high risk of deficiency should receive the following supplementation doses for 6 months; infants (1mg/kg/d), children (15mg/d), adults (25mg/d). [103-110]
Q. 9.5.3	**What is the safe upper limit for zinc supplementation in CF?**
R 9.5.3	UNGRADED. Insufficient evidence to make a recommendation.

PP 9.5.2 and 9.5.3	Suggested supplementation doses.
	• Infants (<2yrs) with persistent failure to thrive and/or those with severe steatorrhoea:
	  ○ Consider a trial of zinc supplementation
	  ○ 1mg elemental zinc/kg/d in divided doses for 6 months (max 15mg/day).
	• Children with suspected zinc deficiency:
	  ○ 15mg/d for 6 months
	• Adults with suspected zinc deficiency:
	  ○ 25mg/day for 6 months
	• In vitamin A deficiency refractory to Vitamin A supplementation, consider an empiric trial of zinc supplementation.
	• The amount of zinc in the CF-specific multivitamin, VitABDECK®, is not adequate to correct zinc deficiency and additional zinc is likely required.
	• The main dietary source of zinc are animal foods as well as zinc fortified cereals
	• Where practical, zinc is best tolerated if given in divided doses

Chapter 10 **Pancreatic Enzyme Replacement Therapy (PERT)**	
Q 10.1.1	**Does gastric emptying rate impact PERT efficacy in people with CF?**
R 10.1.1	GRADE C. Gastric emptying rate may impact PERT efficacy and should be considered in people with CF. [111,112]
Q 10.1.2	**Does the timing of PERT administration in relation to a meal impact PERT efficacy in people with CF?**
R 10.1.2	GRADE D. Limited evidence suggests PERT is equally effective when taken before or after a meal in individuals with CF. It also suggests that for some individuals, changing PERT timing in relation to a meal may improve PERT efficacy. A change of PERT timing can be considered for people with symptoms of fat malabsorption or poor growth once other treatment strategies such as adherence have been taken into account. [112]
PP 10.1.1 and 10.1.2	Prior to changing the timing of PERT in patients with symptoms of fat malabsorption and poor growth evaluate: • Is the patient compliant with PERT? • Is PERT distributed appropriately according to fat content? Explore the role of gastric emptying rate and referral to a gastroenterologist for consideration (± formal gastric emptying assessment). People with fast gastric emptying may benefit from taking PERT before a meal.
Q 10.1.3	**How should PERT be dosed for people with CF to support optimal fat absorption?**
R 10.1.3	GRADE D. There is inconsistent and insufficient evidence to recommend specific doses of PERT required to support *optimal* fat absorption in individuals with CF. A wide range of doses have been shown to be effective. [113-131]
PP 10.1.3	**PERT Dosing Recommendations** Dosing recommendations adapted from international recommendations: • *2006 Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis*[1] • *2008 Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency*[132] • *2009 Cystic Fibrosis Foundation evidence-based guidelines for the management of infants with cystic fibrosis*[87]. • *2016 ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis*[78] **Infants** • Breastfeeds and Infant Formula o Initiate at 2500-5000 IU lipase per breastfeed or formula feed and adjust up according to weight gain and bowel symptoms to a maximum of 10 000 IU lipase/kg/day* • Solids o Approximately 2000 IU lipase/g fat o Maximum 10 000 IU lipase/kg/day* **Children and Adults** • 500-4000 IU lipase/g fat. Maximum 10 000 IU lipase/kg/day* **General PERT recommendations** • Aim for the lowest effective dose • Use an individualised approach • Distribute the enzymes throughout the day according to the fat content of food and drinks consumed • Monitor weight, growth and bowel symptoms • Individuals should be encouraged to discuss PERT with clinic staff before increasing dose • Branded PERT preparations should be used

	Distribution Ensure PERT is correctly distributed over the day's meals based on the fat content of food and drinks consumed **Administration** • Capsules should be swallowed whole or the granules mixed in with an acidic fruit puree – e.g. apple puree. Granules should not be chewed • PERT should be given with all meals, snacks and food containing fat • PERT may be given before, during or after a meal** **Physical Storage** Store capsules in an airtight container in a cool, dry place – see specific product information for more information on storage. Ensure capsules have not exceeded the expiry date * In some situations the upper limit may need to be exceeded in the short term, such as infants feeding frequently – this should be done with caution and with regular review by a gastroenterologist and dietitian **new recommendation
Q 10.1.4	**Is there evidence to support the use of acid suppression medications to improve PERT efficacy for people with CF?**
R 10.1.4	GRADE C. There is inconsistent and limited evidence to support for or against the use of acid suppression medication to improve PERT efficacy by increasing fat absorption for individuals with CF. Further research is required. [133-135]
PP 10.1.4	Take into account the following prior to commencing acid suppression medication in people with CF with symptoms of steatorrhoea and on high dose PERT: • Is the patient adherent with PERT? • Is PERT distributed appropriately according to fat content? • Role of gastric emptying rate and referral to a gastroenterologist for consideration (± formal gastric emptying assessment) • Increasing the dose by stepwise increments to a maximum of 10 000 IU lipase/kg/day • If a trial of acid suppression medication is commenced review its effect regularly, e.g. 3-6 monthly
Q 10.1.5	**What are the risks and long-term health implications associated with phthalate exposure via PERT to people with CF?**
R 10.1.5	UNGRADED. Insufficient evidence to make a recommendation
PP 10.1.5	Provide people with CF and their families with the latest information regarding phthalates and PERT on request. Phthalate polymers, including hypromellose phthalate (HMP), are non-active ingredients in the enteric coating of many medications, including all Creon® products available in Australia and NZ. • Unlike other phthalates that degrade to potentially harmful monoesters, phthalate polymers are considered to be of low or no known toxicity risk. • In Australia the Therapeutic Goods Administration (TGA) lists phthalate polymers as an ingredient for use in prescription medications without any restriction (www.tga.gov.au). All PERT products in Australia are approved by the TGA for use, therefore concern about phthalates is not an indication on its own for changing the choice of PERT preparation. Exploring such a change for an individual should be based on factors such as adequacy of control of malabsorption, and/or the occurrence of side effects. Panzytrat 25 000® does not contain phthalates or the HMP polymer.

Chapter 11 **Gastrointestinal and Hepatobiliary Considerations**	
Gastro-oesophageal Reflux	
Q 11.1.1	**What are the nutrition considerations for the management of gastro-oesophageal reflux (GOR) in CF?**
R 11.1.1	GRADE D. Specific dietary factors that influence the occurrence, severity and management of GOR in CF have not been identified. Further research into the impact of dietary factors on reflux in CF is warranted. [136-139]
PP 11.1.1	• GOR is common in children and adults with CF and can present as either symptomatic or asymptomatic. • The Mayo GER questionnaire (GERQ) and the Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS) are both validated self-administered questionnaires that have been used to record reflux symptoms and severity in the general population. • There are no established guidelines for the diagnosis and treatments of GOR specific to CF. Use clinical judgment when applying GOR guidelines for general population to individuals with CF. • Pharmacological therapy options to reduce the symptoms of GOR are often first choice of treatment. These include histamine receptor antagonists (H_2 antagonists) and protein pump inhibitors (PPIs). • If dietary interventions are considered, take an individualised approach whereby nutritional adequacy is not compromised or unnecessarily restricted. • Supine positioning may exacerbate GOR. Review bed head elevation, feed volumes and rate of feeding to optimise tolerance and reduce the risk of symptoms. Assess reflux symptoms prior to enteral feeding. • Surgical intervention (fundoplication) may be explored if symptoms have not been controlled by pharmacological, dietary or lifestyle interventions. It is important for the interdisciplinary team to evaluate the potential risks and benefits of the surgery for each individual.
DIOS and Constipation	
Q 11.2.1	**What are the nutrition considerations for the prevention and management of Distal Intestinal Obstruction Syndrome (DIOS) in CF?**
R 11.2.1	GRADE C. Inadequate PERT, including poor adherence and under-dosing, is unlikely to play a role in DIOS but should still be assessed as part of an overall dietetics review in CF. The impact of diet, particularly fibre and fluid intake on DIOS is unclear. Further research in the Australian and New Zealand context, particularly in regards to the impact of hydration on DIOS is required. While not examined in the current body of evidence, the impact of sodium intake on hydration and DIOS is warranted in future research. [140-142]
Q 11.2.2	**What are the nutrition considerations for the prevention and management of constipation in CF?**
R 11.2.2	GRADE D. There is inadequate evidence to recommend nutrition considerations in the prevention and management of constipation in CF. Until further evidence is available, complete a thorough diet history, including assessment of hydration (fluid and sodium intake) as well as fibre intake. Review PERT to optimise absorption. Further research in the Australian and New Zealand context is warranted, particularly in regards to hydration (including sodium intake) and constipation in CF. [143]

PP 11.2.1 and 11.2.2	• Medical treatment is a priority, particularly for the diagnosis and management of DIOS. • Surgical intervention is rarely required. • Polyethylene glycol (PEG) laxatives are usually used for the treatment of constipation and are often a first line treatment for DIOS. Many patients continue on laxatives after the resolution of DIOS. • Optimise fluid and salt intake as well as fat absorption in those who present with or have a history of constipation and DIOS. • Patients with complete DIOS may be fasted during initial treatment. In most cases this is short term, however, monitor patients for risk of malnutrition. Total parenteral nutrition (TPN) may be required for more complex cases that do not resolve in a few days. • The Bristol stool chart can be used when assessing bowel patterns in CF. A paediatric version is also available when trying to engage younger children. **Laxatives**: • Insufficient evidence to assess the relative effectiveness or tolerability of different classes of laxatives. Considerations when choosing an agent should include hardness of the stool, potential adverse effects, effectiveness of previous treatments and patient preference. • Adjust laxative regimens according to response and tolerability. • Osmotic laxatives draw water into the stool to help soften the stool and washout the colon. The active ingredient in most osmotic laxatives is usually Polyethylene glycol (PEG). Lactulose, a non-absorbable sugar, is another osmotic laxative used in CF but is often associated increased abdominal pain/cramping. • Stool lubricants help lubricate the bowel wall & soften faecal mass to allow the faecal mass to transit through the colon. NOTE - Mineral oils should not be used for the treatment of DIOS & constipation in children less than 12 months of age. Potential side effects of longer term use in children greater than 12 months of age include: • Possibility of reduced fat soluble vitamins. • Abdominal cramps • Risk of aspiration if used during period of respiratory exacerbation or if the child is fighting the dose.
Colon Cancer Screening	
Q 11.3.1	**What are the nutrition considerations for colon cancer screening in CF?**
R 11.3.1	UNGRADED. Insufficient evidence to make a recommendation.
PP 11.3.1	People with CF have a greater risk of developing colon cancer than the general population. Individual centres need to develop local guidelines with regard to screening older adults to assess risk of colorectal cancer. • More extensive colonoscopy preparation may be required and further research is required.
Liver Considerations	
Q 11.4.1	**Should vitamin K supplementation be recommended for all people with CF-related liver disease?**
R 11.4.1	UNGRADED. Insufficient evidence to make a recommendation – follow recent consensus guidelines. [144]
PP 11.4.1	The risk of vitamin K deficiency is increased in people with CF-related liver disease. Clinicians should base supplementation on the most recent recommendations for vitamin K supplementation in CF [78,144]: • Routine daily supplementation for all PI patients • Infants: 300 – 1000µg/d • Children (>1year) and adults: 1000 - 10 000 µg/d

Q 11.4.2	**What are the requirements for effective supplementation in episodes of vitamin A deficiency in peoples with CF-related liver disease?**
R 11.4.2	UNGRADED. Insufficient evidence to make a recommendation – follow recent consensus guidelines. [144]
PP 11.4.2	Supplement with high oral doses between 5000 – 15 000IU/day (1500ug - 4500ug/d) with the aim of achieving the normal range of serum retinol for healthy individuals. Use caution when giving doses above 20 000 IU/d (6000ug/d) preformed vitamin A if RBP is low. A low retinol : RBP molar ratio may indicate deficiency but further increase in supplementation of preformed vitamin A may be toxic to the liver. Although not routinely available we recommend increased supplementation with β-carotene in these circumstances. Monitor serum retinol and retinol binding protein to ensure the adequacy of therapy to prevent deficiency as well as fasting serum retinyl ester concentration to assess for toxicity.

Chapter 12 **CF-related Diabetes**

No PICO questions were formulated for Chapter 12. This is an area of limited evidence specific to CF, with most international recommendations being formed by expert opinion.

Key Points

- CF-related diabetes shares features of type 1 and type 2 diabetes but is a distinct form of diabetes classified as "other forms of diabetes" or pancreatogenic diabetes. [145,146]
- CF-related diabetes is at the end of a spectrum of progressive glucose tolerance abnormalities; it may occur intermittently, and few people with CF demonstrate completely normal glucose tolerance [147,148].
- Annually screen for CF-related diabetes by 2 hour oral glucose tolerance test and commence insulin early.
- Energy, protein and fat intake targets remain the same as for those without CF-related diabetes (see Recommendations 7.1.1, 7.1.2, 7.1.3 and the corresponding practice points, Chapter 7)
- Assess the quantity (eg. grams of carbohydrate consumed at usual meals / snacks / supplements) and quality of carbohydrate intake (the glycaemic index (GI)) of the carbohydrates at meals and snacks.
- The blood glucose levels pre-meal and 2 hours post-meals should be assessed to assist with planning an insulin regimen in conjunction with the Endocrinologist and planning diet modifications.
- For most people with CF-related diabetes in Australia and New Zealand the HbA1c treatment goal is <7% or <53 mmol/mol, individualise goal as required.
- Annually screen for diabetic complications including hypertension, hyperlipidaemia and neurologic assessment.
- From 5 years after CF-related diabetes diagnosis, screen for complications including nephropathy and retinopathy

Chapter 13 **Bone Health**

Q 13.1.1	**How and when should bone mineral content and density be assessed for people with CF?**
R 13.1.1	UNGRADED. Insufficient evidence to make a recommendation specific to CF. Health professionals should follow consensus document recommendations for assessing bone mineral density for people with CF. [149]

PP 13.1	*2006 Australasian Clinical Practice Guidelines for Nutrition in CF:* Assess bone mineral density periodically in people with CF who are more than eight years of age[1]. Dual energy X-ray absorptiometry scanning is the current gold standard assessment tool. Follow up: Frequency of follow-up scanning is dependent on previous bone mineral density results, type of treatment that was initiated to improve bone mineral density and the emergency of additional risk factors of bone disease. When clinical status is stable, follow-up scanning should be conducted at least: • every three to five years if bone mineral density was normal; Z or T scores > -1 • every two years if bone mineral density was moderately reduced; Z-score between –1 and –2; or T-score between –1 and –2.5, and • annually if bone mineral was severely reduced; Z-score <-2 or T-score <-2.5. More frequent DEXA scanning is suggested if significant new risk factors emerge (e.g. prolonged corticosteroid exposure)
Q 13.1.2	**Is there an ideal serum 25-hydroxyvitamin D level to aim for in people with CF?**
R 13.1.2	UNGRADED. Insufficient evidence specific to CF for the ideal serum 25-hydroxyvitamin D level. It is suggested that the general Australian and New Zealand goal of ≥50 nmol/L be used with a caveat for the time of year at which testing occurs.
PP 13.1.2	It is suggested that the general Australasian goal of ≥50 nmol/L serum 25(OH)D be used if measuring vitamin D at the end of winter or in early spring. If testing at other times of year, aim for a level 10-20nmol/L higher (≥60-70nmol/L).
Q 13.1.3	**What are the calcium requirements in CF to reduce the risk of low bone mineral density?**
R 13.1.3	GRADE D. Calcium requirements to reduce the risk of low bone mineral density in CF are unknown. At this time, health professionals should aim for the RDI when making calcium recommendations in CF. [150]
Q 13.1.4	**Does supplementing calcium above the RDI improve bone mineral density in CF?**
R 13.1.4	GRADE D. There is insufficient evidence to support that routine calcium supplementation above the RDI will improve bone mineral density in CF. Consider calcium supplementation only when dietary intake is unable to meet the RDI. [151]
PP 13.1.3 and PP 13.1.4	Foods high in calcium include dairy foods (e.g. cow's milk, cheese & yoghurt), fortified dairy alternatives (i.e. soy milk), firm tofu & bony fish. Legumes, nuts and some green vegetables also contain small amounts of calcium. More information regarding the RDI for calcium can be found via the Nutrient Reference Values for Australia & New Zealand webpage - *http://www.nrv.gov.au/*

Chapter 14 **Special Considerations**	
Pregnancy	
Q 14.1.1	**What are the nutrition considerations of the management of pregnancy in CF?**
R 14.1.1	UNGRADED. Insufficient evidence to make a recommendation
PP 14.1.1	• Before pregnancy a BMI greater or equal to 22kg/m^2 is recommended. • Undertake a comprehensive nutrition assessment prior to conception and ongoing during pregnancy and post-partum, including standard pregnancy counselling around food safety, alcohol, caffeine and fish consumption recommendations as per Australian [152] and NZ recommendations [153].

	• Clinicians should be guided by local country recommendations for supplementation amounts of folic acid. Assess the need for additional supplementation of 5mg folic acid per day in women with risk factors such as family history of neural tube defects, taking certain medications or with insulin dependent diabetes. • Screening for gestational diabetes mellitus is recommended via a 2hr 75g fasting OGTT when pregnancy is confirmed, at 12-16 weeks and 24-28 weeks gestation. Screen for CF-related diabetes at 6-12 weeks post-partum. • Measure levels of fat soluble vitamins A, D and E at first review after pregnancy confirmation and the beginning of the second and third trimesters. Monitor levels and supplement to maintain in the reference range (refer to PP 14.2 for specific information about vitamin A supplementation). • Undertake iron studies at 20 weeks' gestation and assess the need for supplementation if deficiency is developing. Tolerance of supplementation can be problematic in pregnancy further aggravating gastrointestinal symptoms especially constipation. Preventative management strategies including use of stool softening agents can be helpful. • Weight gain of at least 11 kg has been recommended for women with CF. If nutritional status cannot be optimised by a high energy diet alone, explore oral nutrition supplements or enteral nutrition support. In those requiring tube feeding for the first time; it is best commenced early in pregnancy when best tolerated • It is important to discuss infant feeding options during pregnancy with women with CF. Breast feeding in the mother with CF can be successfully undertaken, however close monitoring of nutritional status and fatigue should be undertaken • It is important to monitor the weight of the woman with CF post-partum. Significant weight loss due to breastfeeding, and potential time burden that may compromise self-care can impact on overall health. Optimising nutrition at this time is vital. • For any complex issues in the pregnant woman with CF, consult a CF specialist adult centre.
Q 14.1.2	**What recommendations around vitamin A supplementation and monitoring should be provided to women with CF who are pregnant or planning a pregnancy?**
R 14.1.2	UNGRADED. Insufficient evidence to make a recommendation
PP 14.1.2	• Measure fat soluble vitamin A level at first review after pregnancy confirmation and at the beginning of the second and third trimesters. • If normal vitamin A levels, supplementation should continue at a dose <10,000 IU/day of retinol. These levels are in line with recommendations for the healthy population in pregnancy. • Reassure the woman that supplements are being prescribed to prevent vitamin A deficiency which like vitamin A excess, is also teratogenic. • If vitamin A levels are high, it is recommended to reduce vitamin A supplementation. A different multivitamin supplement may be required with lower vitamin A (particularly preformed vitamin A, retinol). Assess adequacy of other fat soluble vitamins if the CF-specific multivitamin is ceased. • More frequent monitoring of vitamin A levels may be required following changes to supplement formulation and/or dose. • Review dietary intake of vitamin A including oral and enteral supplements with particular attention to high retinol sources. • Review all non-prescription, over the counter supplements with particular consideration for high retinol supplements (e.g. cod liver oil).
Genetic Modulator Therapies	
Q 14.2.1	**What are the implications of Ivacaftor on nutritional status in children >2 years and adults with cystic fibrosis who have at least one G551D or other gating mutation allele?**
R 14.2.1	GRADE A. There is evidence to suggest that continued use of Ivacaftor therapy leads to significant improvements in weight and BMI in adults and children > 2 years. [154-161]

Q 14.2.2	**Are there any other nutritional considerations (energy, salt intake) that practitioners should take into consideration for people on Ivacaftor therapy?**
R 14.2.2	GRADE D. Well-nourished individuals on Ivacaftor therapy may benefit from a diet more in line with the general healthy population recommendations, although at this stage there is insufficient evidence to recommend routine changes of energy and salt intake for people with CF receiving this medication. [154-163]

PP 14.2.1 and 14.2.2	• Practitioners need to proactively monitor weight gain patterns throughout the first few years of Ivacaftor therapy so that nutritional recommendations can be tailored to the rapidly changing body composition.
	• People with CF-related diabetes are at risk of experiencing hypoglycemia, especially upon commencement of Ivacaftor – monitor blood glucose levels closely
	• The relationship between sodium intake and sweat chloride levels is currently unknown. There is not yet clear evidence for a change in salt supplementation requirements, but provide advice on sodium requirements based on the person's signs and symptoms of salt depletion.
	• Genetic modulators should be taken with a fat containing meal or snack
	  ○ People who are PI should also take their PERT at this time
	• Children:
	  ○ After establishment of Ivacaftor ensure that catch up growth is achieved before considering altering a child's diet in terms of energy and/or salt.
	• If the course of CF lung disease is altered (e.g. a reduction in exacerbation frequency), an individual's nutritional status or dietary intake pattern may also change if overall nutritional requirements are lowered or appetite/intake becomes more stable. A reduction in overall energy intake may not be a concern if adequate nutritional status is maintained, however attention to diet quality may be required.

Q 14.2.3	**What is role of gastrointestinal and/or other nutritional outcome measures in individuals with CF receiving Ivacaftor therapy?**
R 14.2.3	UNGRADED. Insufficient evidence to make a recommendation
PP 14.2.3	Gastrointestinal outcome measures such as faecal elastase and intestinal fat absorption are appropriate to use in this population group. Use of these tests may help guide practitioners in what are appropriate concurrent nutritional therapies (i.e. PERT and protein pump inhibitors). As genetic modulator therapies are relatively new, it is possible that a range of clinical and symptomatic observations will be made, about which more evidence to guide practice recommendations may emerge in the future in relation to modulation or restoration of physiological functions affected by CFTR. There is limited evidence to date of the impact of other CFTR modulator therapies on gastrointestinal function or nutritional outcome measures. Until such evidence is available, identify and evaluate any changes in gastrointestinal or other symptoms in people taking CFTR modulator therapies.

Chapter 15 **Complementary Nutrition Therapies**	
Probiotics	
Q 15.1.1	**Does dietary supplementation with probiotic genus *Lactobacillus* improve nutritional and/or respiratory status in people with CF?**
R 15.1.1	GRADE C. Dietary supplementation with a *Lactobacillus* genus probiotic (single or as part of a mixture) may have health benefits for people with CF, particularly in regards to intestinal inflammation, the intestinal microbiota and risk of pulmonary exacerbation. [164-171]
Q 15.1.2	**Should routine or targeted use of probiotic supplements be recommended for people with CF?**
R 15.1.2	GRADE C. The body of evidence to support health benefits from probiotic supplementation in CF is growing, however there is insufficient high quality evidence to support the *routine* or *targeted* supplementation of probiotics in individuals with CF. [164-171]

PP 15.1 and 15.1.2	**Mechanism of action** • Probiotics are used as a therapeutic option to modulate the composition and actions of the gut microbiota. **Probiotic species, strain and dose** • Mechanism of action and efficacy are strain specific. • Insufficient evidence to recommend any particular probiotic species or strain, single or mixed, as being superior for beneficial health outcomes in CF. • The beneficial dose of probiotics varies depending on the particular species and strain used and the reported benefit – in most cases dose and duration should be based on manufacturer's recommendation. **Other considerations** • Impact on burden of treatment and medication adherence. • Cost – probiotics can be expensive and not subsidised in Australia or New Zealand. • Concerns regarding reported variability in quality control, efficacy and viability of probiotic microbes in different products. • Storage – probiotics are sensitive to temperature, air, light and moisture and often require refrigeration. • Probiotics are often marketed via their trade name (e.g. *Lactobacillus rhamnosus* is marketed as *Lactobacillus GG).* • Recommend that if trialled, probiotics are taken for at least 4 weeks. If after this time they have no impact on symptoms, cease or trial an alternative preparation. • Potential health benefits are thought to subside shortly after supplementation is ceased. • Use probiotics with caution with high risk patients such as those with severe respiratory function. • Care should also be taken administering probiotics to those with venous catheters due to risk of sepsis.
Glutathione	
Q 15.2	**Does antioxidant supplementation with oral glutathione or N-acetylcysteine improve nutritional and/or respiratory status in CF?**
R 15.2	GRADE C. Dietary supplementation with oral antioxidant glutathione or N-acetylcysteine may improve nutritional status in individuals with CF. There is inconsistent evidence to suggest that dietary supplementation of either of these constituents improves respiratory status. The currently available evidence does not support the use of glutathione therapy in people with CF [78,172-176]
PP 15.2	**Mechanism of action** • Glutathione is a water-soluble antioxidant. • N-acetylcysteine provides the amino acid cysteine (non-essential amino acid) for systemic glutathione replenishment. **Sources of supplementation** • Dietary sources of cysteine include meat, dairy, poultry, fish and soy-based products. • There is insufficient evidence to support the use of glutathione therapy in CF. **Other considerations** • Impact on burden of treatment and medication adherence

Coconut Oil	
Q 15.3	**Is there evidence that dietary supplementation with coconut oil improves nutritional status in pancreatic insufficient people with CF?**
R 15.3	UNGRADED. Insufficient evidence to support a recommendation.
PP 15.3	Coconut oil composition: • Lauric acid (45 - 48%) – medium chain triglyceride (MCT) • Myristic acid (14 - 18%) – long chain triglyceride (LCT) Lauric acid is considered a MCT, however, it is metabolised differently. In digestion, lauric acid behaves more like a long chain fatty acid. Commercially manufactured MCT oils are generally derived from coconut or palm oils and contain approximately 95% MCT.
Herbal Suppliments	
Q 15.4	**Is there evidence that dietary supplementation with specific herbal products or their components improves health outcomes in individuals with CF?**
R 15.4	GRADE D. There is no evidence that dietary supplementation with specific herbal products or their components improve health outcomes in individuals with CF [177]
PP 15.4	People with CF should be encouraged to discuss herbal and complementary therapies with their interdisciplinary CF team prior to commencing any form of supplementation. Specific enquiry by the CF pharmacist or dietitian may be helpful. Limited evidence surrounding dosing, safety or efficacy of most herbal supplements.

Chapter 16 **Lung Transplantation**

No PICO questions were formulated for Chapter 16. This is an area of limited evidence specific to CF, with most international recommendations being formed by expert opinion.

Key Points

Pre-transplantation

- Care should be overseen by the local CF team with the aim of maintaining nutritional status (i.e. BMI ≥ 18.5 kg/m^2 to 35 kg/m^2)
- Once listed for transplantation close liaison between the CF team and the transplant team is essential

Post-transplantation

- Post-transplant care is generally coordinated by the specialised transplant unit.
- Nutritional management in the immediate post-operative period should focus on attaining adequate protein and energy intake [178]
- Post transplantation there is potential for additional nutrition related issues such as bowel management, GOR, delayed gastric emptying, diabetes, lipid abnormalities, bone disease and renal disease
- Medications used to prevent lung transplant complications (e.g. antibiotics, immunosuppressants and anti-fungal medications) can have marked nutrition-related side effects, including taste changes, nausea, vomiting and diarrhoea
- Longer term post transplantation energy and vitamin requirements (i.e. vitamin A and E) are often reduced, thus regular biochemistry and monitoring by a dietitian is essential

CHAPTER 1 INTRODUCTION

N. Saxby, P. O'Neill & S. King

The '2017 *Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand*' is an up-to-date resource that addresses the many aspects of the nutrition management of cystic fibrosis (CF). Whilst the '*2017* Guidelines' were designed to be utilised by the entire CF care team including consumers, the dietitian's role within the interdisciplinary team is emphasised. Practice recommendations are evidence-based, developed through use of systematic review processes and with consumer and clinical stakeholder consultation.

1.1 Background to the Guideline Update

The '*2017 Guidelines*' are a result of a planned update of an earlier version, the '*2006 Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis*', which were endorsed by the Dietitians Association of Australia (DAA). Key differences between the 2006 Guideline and the current version include a move towards an interdisciplinary approach to CF nutrition, the acknowledgement that new genetically targeted CF therapies have diverse nutrition implications for the CF population (e.g. genetic modulators), and an overview of dietitian prescribing in New Zealand (NZ). Consumer consultation also led to the inclusion of omega-3 fatty acids (Chapter 7) and a section on complementary nutrition therapies (i.e. glutathione, probiotics, curcumin, garlic and coconut oil) (Chapter 15).

In a series of surveys (1998, 2005 and 2010), Australian and NZ CF dietitians have shown increased alignment with dietetic practice recommendations [179]. The 2005 survey was specifically undertaken to provide baseline data on nutrition and dietetic practice in Australia and NZ prior to the implementation of the 2006 guidelines [180]. A repeat survey (2010, unpublished) aimed to document and compare CF nutrition management practices before and after the release of the 2006 guidelines. Results from the 2010 nutrition practice survey (which covered 3548 people with CF in Australian and NZ, n=37 centres) showed that general nutrition advice regarding a diet high in energy, fat and salt and the use of pancreatic enzyme replacement therapy has remained consistent since 2005. Improvements in consistency of dietetic practice were seen in the routine monitoring of fat soluble vitamin levels and screening for CF-related diabetes; however, significant variability in dietary management of CF-related diabetes remained.

1.2 Purpose, Goals and Objectives

This guideline document has been created to:

- ensure current best-practice guidelines for management of nutrition and pancreatic enzyme replacement therapy (PERT) are accessible to all health professionals providing care to individuals with CF and their families/whanau;
- ensure the nutritional and PERT education and care provided to all infants, children and adults with CF is evidence based where possible, and reflects current knowledge;
- standardise the nutritional and PERT care of infants, children and adults with CF;
- be widely and readily available in order to support isolated practitioners; and
- promote nutritional and PERT care as a priority in service provision to individuals with CF.

The **goals** of the guideline document are to:

- facilitate optimal outcomes for all infants, children and adults with CF by promoting best practice in clinical nutrition; and
- promote consistency and equity of healthcare and evidence based practice throughout Australia and NZ.

The **objective** of this guideline is to provide guidance to practitioners to enable them to:

- implement comprehensive and timely nutrition assessments in order to improve and maintain healthy living standards and identify nutritional deterioration early;
- optimise the management of nutrition and PERT, including the management of concurrent diseases and complications;
- support people with CF to achieve and maintain optimal nutritional status;
- encourage individuals with CF to follow a healthy diet tailored to their individual CF needs and to have positive eating behaviours; and
- improve quality of life of the person with CF, their carer/carers, and family/whanau.

1.3 Scope

The **target population** of these guidelines is all individuals with CF cared for within the Australian and NZ healthcare systems. The document will be applicable across all age groups. Differences in nutritional and health-related issues, management or recommendations for different age groups, disease stages, cultures or geographical conditions within the target countries will be indicated within the document, or addressed separately for different groups.

The **target audience** for these guidelines is all health practitioners who work with people with CF, particularly dietitians. This includes specialist CF centre dietitians, regional/shared care dietitians and other members of interdisciplinary CF teams. These guidelines will also aid the training and teaching of dietetic and medical students as well as locum dietetic staff.

As people with CF receive nutrition care in both inpatient and ambulatory care settings, these guidelines are to be used in all settings.

1.4 Sociocultural Considerations

These guidelines are likely to have negligible impact in Aboriginal and Torres Strait Islander populations, as CF almost always affects Caucasian populations. Supportive low literacy consumer resources will be developed for those (small minority) where English is a second language.

In New Zealand, 7% of the CF population identifies as Māori,[181] less than the 15% reported for the general population. There are currently no additional CF-specific issues that have identified as relevant to the CF Māori population. The Code of Ethics for NZ dietitians acknowledges the relevance of the Treaty of Waitangi in the delivery of dietetic services to all New Zealanders and honours the principles of partnership, protection and participation as an affirmation of the Treaty of Waitangi [182]:

- **Partnership** involves working together with iwi, hapū, whānau and Māori communities to develop strategies for Māori health gain and appropriate health and disability services.
- **Participation** requires Māori to be involved at all levels of the health and disability sector, including in decision-making, planning, development and delivery of health and disability services.
- **Protection** involves the Government working to ensure Māori have at least the same level of health as non-Māori, and safeguarding Māori cultural concepts, values and practices (See http://www.health.govt.nz/our-work/populations/maori-health/he-korowai-oranga/strengthening-he-korowai-oranga/treaty-waitangi-principles).

CHAPTER 2 METHODS

N. Saxby, T. Crowder, P. O'Neill, C. Painter, L. Guest, J. Heyward & S. King

2.1 Development of Practice Questions

The first drafts of practice questions, in PICO format, were written in collaboration with dietitians from Australia and New Zealand in 2012. Further input and refinement was obtained from the dietitian authorship group and the inter-disciplinary clinical expert committee.

A summary list PICO of questions covered in this guideline are located in the accompanying administration report.

2.2 Systematic Search Strategy

Electronic databases (Embase, CINAHL, PubMed, AustHealth, and Cochrane) were searched from January 2002 to August 2015 for each clinical practice question. Key recently published research, after August 2015, was also included if it was of vital significance to recommendations and/or practice points. This broad search strategy was developed by the project co-chair with assistance from the methodological experts and appropriately trained medical librarians.

Up until June 2015, all systematic literature searches were completed by either the project co-chair or one of the project facilitators. In July 2015, in an effort to enhance the literature search process, a medical librarian assumed responsibility of completing the remaining literature searches. Between January 2012 and June 2016, twice yearly automatic updates of new literature that met the search criteria were set up to ensure that final guideline recommendations were contemporary at the time of publication.

2.3 Screening of Literature Results

All retrieved literature searches underwent a two stage screening process against predefined inclusion and exclusion criteria.

FIRST SCREENING

The first screening round was completed by one or two of the project co-chair / project facilitators. Screening involved review of titles and abstracts of all retrieved journal articles. All irrelevant, incorrect, non-English and duplicates were removed.

SECOND SCREENING

Full articles were then retrieved and a second screen was undertaken. The section leader of the topic and one other group member assessed each article for inclusion against the predefined inclusion and exclusion criteria for each PICO question. See technical report. Journal articles meeting the inclusion criteria were then forwarded to members of the dietitian steering group for critical appraisal and data extraction.

2.4 Literature Critique, Development of Evidence Statements and Grading of Recommendations

Each journal article was appraised independently by two members of the authorship group for level of evidence and quality. Levels of evidence were rated using the NHMRC criteria as shown in table 2a and quality rankings assigned using the American Dietetic Association tool as shown in table 2b and table 2c (i.e. positive, neutral or negative quality) [183,184]. If consensus was unable to be reached after the first review, the dietitians critiquing the evidence were asked to complete a second review, and if required a third reviewer (i.e. methodological expert) critiqued the article and acted as an arbitrator.

The body of evidence for each practice question was synthesised into an evidence statement and rated using the NHMRC evidence matrix as shown in table 2d[183]. When forming the practice recommendations, consideration was given to the volume of evidence, consistency of results and potential clinical impact. Generalisability and applicability of the recommendation to the Australian and New Zealand healthcare context was also considered, including relatability to both the '*Cystic Fibrosis Standards of Care for Australia*' and '*Cystic Fibrosis Standards of Care New Zealand*'[2,3].

A summary spreadsheet was developed to collect and collate the evidence and quality summary statements for each clinical practice question. For brevity of the guidelines, these spreadsheets can be found in the companion technical report titled '*Providing the evidence for the 2017 Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand*'.

Table 2a. NHMRC Levels of Evidence for Intervention and Prognosis Studies [183]

Level of evidence	Intervention Study	Prognosis
Level I	Evidence obtained from a systematic review of all relevant randomised controlled trials	A systematic review of level II studies
Level II	Evidence obtained from at least one properly designed randomised controlled trial	A prospective cohort study
Level III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)	All or none (All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect)
Level III-2	Evidence obtained from comparative studies with concurrent control and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial
Level III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel group	A retrospective cohort study
Level IV	Evidence obtained from case studies, either post-test or pre- and post-test.	Case series, or cohort study of persons at different stages of disease

Table 2b. Assessing primary research quality using the American Dietetic Association (ADA) evidence analysis manual [184]

Quality	Definition of Quality for Primary Research
Positive	If most of the answers to the validity questions are yes (including criteria 2,3,6, 7 and at least one additional yes), the report should be designated with a plus symbol (+)
Neutral	If the answers to validity criteria questions 2,3,6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral symbol (Ø)
Negative	If most (six or more) of the answers to the above validity questions are no, the review should be designated with a minus symbol (-)

Table 2c. Assessing review article quality using tools from the ADA evidence analysis manual [184]

Quality	Definition of Quality for Review Articles
Positive	If most of the answers to the validity questions are yes (must include criteria 1,2,3,4), the review should be designated with a plus symbol (+)
Neutral	If the answers to any of the first four validity questions (1-4) is no, but other criteria indicate strengths, the review should be designated with a neutral symbol (Ø)
Negative	If most (six or more) of the answers to the above validity questions are no, the review should be designated with a minus symbol (-)

Table 2d. NHMRC Evidence Matrices and Forming Grades of Recommendation (NHMRC 2012) [183]

Component	A – Excellent	B – Good	C – Satisfactory	D - Poor
Evidence base	-	One or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency	All studies consistent			
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guidelines	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

2.5 Weak/low-quality Evidence and Evidence Gaps

The *'2017 Guidelines'* are mostly based on lower level evidence (i.e. NHMRC recommendation levels C and D). Many nutritional studies are not completed in a blinded fashion. Furthermore, like other areas of CF research, often the sub-group that would have been likely to benefit from intervention were excluded for ethical concerns. Until better quality evidence is available, it is important that lower level evidence is still included to guide best practice.

Poor study quality is another area of concern for guideline developers. A recent review revealed that even when nutritional randomised controlled trials are completed in people with CF that their study quality is often suboptimal[185]. More specifically, nutritional randomised controlled trials (RCTs) are frequently characterised by lower quality methodology, small sample sizes (insufficient to provide clinically meaningful data), have short intervention timelines and fail to examine outcome parameters that are important to people with CF. The evidence matrices located in Chapter 18 will help clinicians to identify where and how lower quality evidence has been included in these guidelines.

Standard practice for the assessment, monitoring and supplementation of fat soluble vitamins and minerals vary internationally. Where evidence is low this guideline includes considerations from a number of international consensus papers. The recommendations have been formulated from the available evidence, international practice and application to the Australian and NZ environments.

STEP 1 PRACTICE POINTS

Where there was insufficient quantity or quality of evidence and recommendations could not be made in the guidelines, practice points developed by consensus of the dietitian authorship group and interdisciplinary clinical expert committee are provided. Dietitians and other disciplines still require guidance to ensure optimal and consistent clinical practice.

STEP 2 CREATION OF POSITION PAPERS

It is anticipated that in 2018, following the release of these guidelines, that a Delphi process will be completed to formally reach consensus across Australian and NZ CF experts in topic areas where insufficient evidence was identified. Recommendations based on this Delphi process will be published separately as a follow-up position statement.

2.6 Background Material and Other Guidelines

Literature used for the background sections (i.e. narrative text) was not systematically reviewed and does not include any clinical recommendations. Background sections were written by the section leaders under direction of the project co-chair and the interdisciplinary clinical expert committee.

Where available and current, existing TSANZ endorsed guidelines and position paper recommendations have been utilised within this guideline. This helps ensure consistency in trans-Tasman clinical practice for people with CF.

2.7 Consumer Participation in Guideline Development

Consumers were involved in the guideline development process from the beginning.

The dietitian authorship group contained two consumer representatives who are also dietitians. In addition, expressions of interest for the interdisciplinary committee initially resulted in three consumer representatives however, due to illness (n=1) and resignation of role at consumer organisation (n=1) numbers of consumers participating in the guideline development reduced to one. Consumer feedback was also sought via occasional newsletter, circulated throughout Australia and New Zealand.

The guideline development process did not include any representatives of Aboriginal and Torres Strait Islanders people. Cystic fibrosis almost exclusively affects the Caucasian population so it was felt this representation was not necessary.

2.8 Peer Review

Comments/feedback on all documents were sought from dietitians not directly involved in this project through the Australian and New Zealand dietetic professional associations (i.e. DAA and DNZ). Drafts of all documents were also circulated for comments/feedback to dietitians working at major CF centres.

A draft of the guideline was also reviewed by members of the TSANZ and content experts as requested by the Clinical Care and Resources Subcommittee (CCRS). Two members of the CCRS committee also critiqued the quality of the final guideline using the AGREEII tool. Additionally, four international clinical reviewers with expertise in nutritional aspects of CF were provided to the NHMRC.

2.9 Public Consultation

The 2017 Guidelines were released for public consultation from 1 December to 31 December 2016. The public consultation process was advertised to the general public (via newspaper advertisement), people with CF (via CFA and CFNZ websites and facebook pages), and health professionals (via TSANZ webpages and email). Submissions were received from health professionals across a number of hospital settings. Comments focused on clarification of content where process or detail was unclear. All comments were considered, and where appropriate addressed or integrated into the final document. Feedback is summarised in a supplementary report titled Summary and response to public consultation feedback.

CHAPTER 3 THE ROLE OF NUTRITION IN CF CARE

S. King, N. Saxby & N. Sander

Cystic fibrosis is the most common lethal autosomal recessive genetic condition affecting Caucasians [186,187]. Over 3500 Australians and New Zealanders live with this condition, with approximately between 80 to 100 new diagnoses in Australia and 10 in New Zealand of CF annually [188,189]. CF is a multi-system condition characterised by abnormally high sweat chloride (and sodium) levels, progressive lung disease, pancreatic insufficiency, as well as hepatobiliary and fertility tract complications. Over 90% of individuals with the condition experience one or more gastrointestinal complications. Optimising growth and nutrition in individuals with CF has been shown to positively influence lung function and survival [190]. This chapter broadly focuses on the role that nutrition plays in CF care.

3.1 Considerations for New Diagnosis

All babies born in Australia and NZ undergo newborn screening for the most common CF-causing genes [2,3]. Most babies with CF (~90%) will be identified using this method [191]. CF may also be suspected in infants who are born with meconium ileus (bowel blockage) and in children and adults who suffer from poor weight gain and suboptimal growth, steatorrhoea or constipation, ongoing sinus issues and/or regular chest infections [192,193]. Individuals who are diagnosed as adults generally have milder forms of CF. Confirmation of a CF diagnosis is made using a sweat test, even in cases where two abnormal CFTR genes are known. Sweat chloride levels > 60mmol/L are diagnostic of CF [192].

People who are newly diagnosed (and their carers/families) require access to a specialist CF team including a specialist dietitian. Promotion of good nutrition is to be commenced as soon as possible and nutrition education is to be provided. Table 3a highlights nutrition considerations for infants, children and adults at time of diagnosis.

Table 3a. Nutritional considerations for people newly diagnosed with CF

Practice considerations to promote good nutrition	
Infants and children	• Conduct a growth assessment. • Pancreatic status is to be promptly assessed and pancreatic enzyme replacement therapy commenced if indicated. • Review fat-soluble vitamin status and liver function. Low fat-soluble vitamin levels can be an early indicator of pancreatic insufficiency. • Encourage and support breastfeeding. Most infants with CF are able to maintain adequate growth while breastfeeding. • The benefits of exclusively breastfeeding a CF baby for the first 6 months include a decreased use of intravenous antibiotics for the first two years of life. • Energy supplements/concentrated infant formula top-ups can be used. • A standard infant formula is usually recommended where breastfeeding is not possible. • Consider routine salt, electrolyte and fat soluble vitamin supplementations.
Adults	• Assess nutritional status and weight history. • Consider if genetic potential for growth has been met. • Pancreatic status is to be promptly assessed and PERT commenced if indicated. • Review fat-soluble vitamin status (A, D, E and K) and liver function. • Consider commencing routine salt and fat soluble vitamin supplementation.

3.2 Effect of Nutrition Status on CF Lung Disease and Survival

The relationship between lung function, survival and nutrition in CF is well established. More specifically, normal body weight is associated with better preservation of lung function [190]. Corey and colleagues (1988) first highlighted the importance of nutrition in their landmark study titled "A comparison of survival, growth, and pulmonary function in patients with CF in Boston and Toronto" [194]. Whilst there was no significant difference in the respiratory care provided at the Boston and Toronto clinics between 1972 and 1981, nutritional management between these two centres varied greatly. In Toronto an aggressive approach to nutrition was recommended (i.e. high fat and high energy diet) whereas the Boston clinic followed standard nutritional practices of the time (i.e. low fat diet to manage symptoms of malabsorption. Toronto's aggressive approach to nutrition resulted in better nutritional status for individuals with CF, and ultimately significantly longer lifespans (median age of survival Toronto 30 years vs Boston 21 years) [194]. A subsequent study showed that after United States of America (US) CF clinics took up the Canadian (Toronto) approach that clinical outcomes were also significantly improved [195]

Of particular clinical interest, however, is that evidence has shown better nutritional status in childhood is associated with improved clinical outcomes (lung function, adult height, fewer CF associated complications) and survival in individuals with CF [196-200]. Poor nutrition has been shown to have adversely impact lung development in pre-adolescent children [196,201]. The pattern of good nutrition and good lung function appears to be lineal, to a certain extent, as individuals with CF grow older [132,190,198,202].

Marked improvements in the nutritional status of CF populations have been demonstrated over recent decades, including in Australian and New Zealand populations. Collins et al reported improvement in the mean height Z-score of 10-15 year olds with CF in Newcastle between 1993 and 1997 from -0.88 to -0.05 [203]. Richardson et al compared adult cohorts from Melbourne in 1983 and 1997, finding height advantages in the 1997 cohort of 8cm and 5cm in males and females respectively, and weight advantages of 13 kg and 12 kg respectively [204]. More recent registry data demonstrates ongoing improvements in the nutritional status of local CF populations and reduction in the prevalence of nutritional deficits. Between 2004 and 2014, the proportion of children with CF in Australia with a height less than the 10th percentile decreased from 19% to 12% [188,205]. Correspondingly, the prevalence of BMI less than the 10th percentile fell from 10.4% to 6.6% and the proportion of adults with a BMI less than 20 kg/m^2 fell from 27% to 20% [188,205].

NUTRITION DEFICITS IN CF

Despite the improvement in the overall nutritional status of CF populations, nutritional deficits are still prevalent. They may be present in people with CF from a young age[1] and may persist throughout life, normalize with intervention, or emerge episodically. While nutritional status in populations diagnosed early, including through newborn screening, is better than in those where CF has been diagnosed later in life, deficits may still be seen in those diagnosed through newborn screening (NBS) programs [1].

Nutrition deficits observed at an individual and/or population level in CF include:

- retardation in weight gain and linear growth in children [197,206,207]
- delayed onset of pubertal growth spurts and lower peak pubertal height velocity compared to healthy population reference values in some [197], but not all [208] studies
- lower height, weight and BMI, whether measured as percentiles, Z-scores or mean adult levels, when compared to healthy population data [204,207,209]
- reduced body fat stores in some individuals [206,210,211]
- reduced fat-free mass (FFM) (also known as lean body mass), whether measured as FFM or using other indices such as total body nitrogen, total body potassium or body cell mass [19,212-219]
- reduced rates of accretion of fat free mass in children over time [206,211]
    - FFM deficits tend to be greater than decreases in fat stores [210,214,220-222]
    - Low FFM stores are not confined to those who are underweight, but may also be seen in those with normal BMI [213,223-226]. This shows that those with normal body weight or BMI cannot be assumed to have normal FFM stores.
    - Despite fat free mass being the major contributor to total body weight, loss of, or gain in, fat-free mass stores cannot be assumed from change in total body weight, as less than 40% of the variability in weight change over time is accounted for by change in FFM [214,227].

It is not possible to synthesise the results of all studies to define the prevalence of reduced fat-free mass due to heterogeneity in terms of the age and disease severity of the study populations, body composition methods, criteria used to define FFM depletion, and the country and the decades in which studies were undertaken.

While risk factors for poor accretion of fat-free mass in childhood and/or fat-free mass depletion in adults are not yet universally accepted, identified correlates of lower fat-free mass include lower forced expiratory volume in 1 second (FEV_1) and higher levels of circulating inflammatory cytokines [19,219,222-224,227,228]. Further research will be required to identify if modification of these associated clinical variables prevents or reverses FFM depletion.

SO, WHAT DOES THIS MEAN FOR PRACTITIONERS?

- Achieving near normal nutritional status for CF populations is now an achievable goal.
- Nutritional deficits are still prevalent in a significant proportion of the CF population and thus surveillance to identify those at risk of undernutrition is a vital component of CF care.
- Nutrition support should be implemented early for people with CF, and regular monitoring and evaluation is vital [78].

3.3 Complications of CF with Nutrition Implications

Concurrent complications and co-morbidities which can place individuals at further risk of poor nutritional status include malnutrition, pancreatic insufficiency and pancreatitis, GOR, constipation and DIOS, CF-related liver disease, intestinal dysbiosis, CF-related diabetes, bacterial overgrowth and dyslipidaemia. Each complication is briefly outlined here – for more detailed information please refer to the corresponding guideline chapter.

UNDERNUTRITION (Chapter 5 and 6)

- Recent figures show that undernutrition affects approximately 6% of adults (BMI<18.5 kg/m^2) and 6.6% of children (BMI<10th percentile) with CF [188].
- Median height and BMI percentiles in children with CF are lowest in adolescence [188]
- Causes of undernutrition are generally multifactorial – physiological and socio-economic.
- Persistent undernutrition is associated with significant morbidity and mortality.
- If not corrected, undernutrition may result in:
    - altered pulmonary defence mechanisms [78]
    - altered pulmonary muscle function [78]
    - decreased exercise tolerance [78]
    - immunology impairment [78]
    - growth defects [229]
    - inadequate accretion of bone minerals [230]

PANCREATIC INSUFFICIENCY AND PANCREATITIS (Chapter 10)

- Pancreatic insufficiency affects up to 90% of people with CF [188,189,205].
    - Being pancreatic sufficient however, still indicates some impairment and is not equivalent to normal pancreatic function [231].
- Some individuals with pancreatic sufficiency are at risk of progressing to pancreatic insufficiency, particularly after the development of recurrent episodes of pancreatitis [232].
- Pancreatic insufficiency is generally associated with more severe CFTR mutations (i.e. class I, II, III) [233].
- Pancreatic insufficiency is a main factor contributing to undernutrition in CF.
- If poorly managed, pancreatic insufficiency can result in nutritional decline in:
    - fat soluble vitamin levels (A, D, E, K),
    - growth and body composition,
    - attainment/maintenance of peak bone mass
    - gastric motility [233]
- Individuals with pancreatic sufficiency have an approximately 20 to 40% lifetime chance of developing pancreatitis [232].

GASTRO-OESOPHAGEAL REFLUX (Section 11.1)

- Reflux is common in both children and adults with CF.
- Reported prevalence rates vary from 20-85%.
- Unique pathophysiology – mechanism includes increased intrathoracic inspiratory pressure from respiratory disease.
- May contribute to respiratory decline through aspiration [233].

DIOS AND CONSTIPATION (Section 11.2)

- DIOS is a specific and unique complication of CF.
- DIOS is characterised by:
  - acute onset of abdominal pain
  - abdominal distention
  - faecal mass in the ileocaecum
  - radiographic signs of distal small bowel distention or obstruction
- Risk factors for DIOS may include suboptimal adherence to PERT and dehydration [234].
- Constipation is very common in CF, and usually presents with a more gradual onset of symptoms and is easier to relieve.
- Altered intestinal fluid composition is considered the main cause of constipation.
- It is very important that clinical teams distinguish between symptoms of chronic constipation and DIOS in individuals with CF [233].

CF-RELATED LIVER DISEASE (Section 11.4)

- CF-related liver disease, predominately liver cirrhosis, is the third leading cause of death amongst individuals with CF. Liver disease may also be expressed as impaired bile flow and/or general hepatic dysfunction.
- CF-related liver disease places individuals with CF at increased risk of malabsorption, undernutrition and fat soluble vitamin deficiencies [233].

INTESTINAL INFLAMMATION (Section 11.5)

- There may be a correlation between poor weight and height measures with gut inflammation [235]
- Intestinal dysbiosis (small intestinal bacterial overgrowth) is common in people with CF however [236] the potential significance of this is not well understood [236,237].

CF-RELATED DIABETES (Chapter 12)

- Prevalence of CF-related diabetes increases with age, with greater than 50% of people being affected at age 40 [238]
- CF-related diabetes has a complex pathophysiology. Loss of pancreatic islet cells lead to both insulin and glucagon deficiency [238].
- CF-related diabetes is associated with worsening pulmonary and nutritional outcomes [239,240].

DYSLIPIDAEMIA (Chapter 7)

- Fatty acid profiles are commonly affected in people with CF [241], specifically:
  - altered serum phospholipid profiles, and
  - low LDL and HDL-cholesterol lipoproteins.
- Fat malabsorption may contribute to abnormal lipoprotein delivery in blood circulation [242].

3.4 Monitoring Nutrition Outcomes

Disease progress in people with CF is monitored in Australia and NZ through the use of data registries - namely, the Australian CF Data Registry (Australia) and Port CF (NZ). The national data registries are overseen by CFA and CFNZ, with each having its own governing committee. Importantly, there is a dietitian representative on both the Australian and NZ data registry governance committees. Dietitian representation helps to ensure appropriate collection and evaluation of nutrition related data.

It is anticipated that continuous improvements will be made to the Australian and NZ CF data registries. In the next five years, dietitians can expect to see more information reported about nutritional parameters. This will allow dietitians to evaluate nutritional status of the CF population (at an individual, clinic, state or country level) to be evaluated against the interventions provided. An advocacy campaign to bring the growth charts used in NZ Port CF system consistent with international practice is also planned.

In Australia dietitians can arrange data registry access via their CF specialist centre director. In NZ access can be arranged through CFNZ.

Table 3b. Comparison of data references for Australian and New Zealand data registries

CF data registries	
Australian CF Data Registry	Uses World Health Organisation (WHO) growth charts for 0-2 year olds and Centre of Disease Control (2000) growth charts for children older than 2 years. **ACFDR Patient summary reports** Provides a visual display of hospitalisations, clinic visits, and trends in pulmonary function and nutrition. Also shows microbiology history over time and current CF-related complications. These reports can be used for pre/post clinic staff meetings and patient/family education.
New Zealand - Port CF	Uses UK-90 growth charts for 0-18 year olds. **PORT CF Patient summary reports** Provides a visual display of pulmonary function and nutrition trends. **Port CF Nutritional summary reports** Provides a narrative summary for practitioners or patient/family use. Reports can be used as a shortcut for calculations of average weight gain per day, average linear growth per year, and enzyme doses.

CHAPTER 4 SERVICE DELIVERY

N. Saxby & T. Crowder

It is noted that health system priorities, resourcing and health professional scope of practice may differ between different regions/countries, and thus it is important that recommendations reflect the local Australian and NZ practice environment and health systems. Where there are differences in recommendations between peak bodies in terms of components and frequency, local standards of care, practices and health service considerations have been used to inform practice recommendations and advice.

4.1 Interdisciplinary Care

Interdisciplinary care is known to deliver the best outcomes for people with CF[243]. Interdisciplinary team approaches, as the word itself suggests, integrate separate discipline approaches into a holistic management plan for the person with CF. In Australia and NZ, care is generally provided by a specialist CF team which includes a nutrition expert, a qualified dietitian [2]. Doctors including gastroenterologists and endocrinologists, nurses, physiotherapists, pharmacists, social workers and psychologists also play important roles in promoting good nutrition. New Zealand CF clinic sizes are significantly smaller than those seen in Australia due to the diverse geographical distribution of people with CF. Despite continuous advancements, treatment for CF remains non-curative and is aimed at optimising lung function and nutritional status [2,244]. Dietitians play an important role in identifying growth and nutrition issues that may be related or unrelated to CF disease and may require specific interventions.

4.2 Dietetic Staffing

What is the level of dietetic service required for people with CF? PICO 4.1

There have been no specific studies looking at dietetic staffing in relation to patient outcomes [un-graded].

Consensus documents from across the world suggest consistent dietetic staffing ratios for smaller clinics, with greater variability being seen in recommendations for centres with more than 150 patients [2,3,244]. It is recommended that staffing levels for dietitians in CF clinics follow current consensus documents, see table 4a (Australia) and table 4b (NZ). Where possible, to ensure continuity, the same dietitian/s should support both outpatient and inpatient CF management [2,3] For larger services, an increase in dietetic staffing that is proportionate to these staffing ratios is likely to be required in order to provide nutrition management in accordance with and these Nutrition Management Guidelines and the CF Standards of Care [2].

Table 4a. Dietitian staffing (full-time equivalents) recommended by Cystic Fibrosis Australia for Australian adult and paediatric CF centres [2].

Staffing	50-75 patients	75-150 patients	≥150 patients
Dietitian	0.5	1	2

Table 4b. Dietitian staffing (full-time equivalents) recommended by Cystic Fibrosis New Zealand for NZ adult and paediatric CF centres [3].

Staffing	Per 10 patients	Per 50 patients sole care	Per 50 patients shared care
Dietitian	0.1	0.5	0.25

*i.e. staffing levels for professionals who visit another centre

4.3 Dietitian Role

A copy of the 2014 CF dietitian role statement can be found in Appendix A. This role statement was developed by the DAA CF interest group in collaboration with the NZ dietitians CF special interest group, thus it is generally applicable for use in both countries. A significant difference in practice between the two countries, however, is that designated dietitians in NZ can prescribe certain nutritional related medications (e.g. pancreatic enzyme replacement therapy) whereas Australian dietitians cannot. Dietitian prescribing in NZ is explained more in section 4.4.

ALLIED HEALTH ASSISTANTS (NUTRITION)

In their 2013 pilot project, the dietetic team at Children's Hospital at Westmead in Sydney demonstrated the benefit of using a nutritional assistant (Cert III Allied Health Assistant) in the care of children and adolescents with CF [245]. The aim of this position was to provide technical support for clinical dietitians in both the outpatient and inpatient setting and ultimately allow the specialist CF dietitian additional time for more complex nutritional interventions. The nutritional assistant was considered part of the interdisciplinary CF team.

Roles and responsibilities of the assistant role included administration (management of home-enteral nutrition and oral/enteral nutrition support funding accounts, pre-clinic growth screening, and dietary food analysis), inpatient services (management of food services and the practical application of diet specifications), outpatient services (nutrition screening, diet histories, design and implementation of education tools, joint dietetics education sessions and the practical implementation of food knowledge), and project work (resource development and quality improvement work in conjunction with the specialist CF dietitians).

4.4 Designated Dietitian Prescribing in NZ

Since December 2011 dietitians have been able to "prescribe" subsidised non-prescription items for therapeutic nutrition for outpatients but not medicines classified as prescription under the Medicines Act 1981. The new Medicines (Designated Prescriber – Dietitians) Regulations 2015 (the Regulations) means that suitably trained dietitians are now able to prescribe a number of products including: pancreatic enzymes therapy, zinc and high dose Vitamin D.

The Board requirements for education and training that Registered Dietitians must undertake before commencing prescribing are as follows:

- a Master of Dietetics degree (University of Otago) or Master of Science (Nutrition and Dietetics) degree (Massey University) or Master of Health Sciences in Nutrition and Dietetics degree (University of Auckland), conferred after January 2014; or
- for all other NZ Registered Dietitians the successful completion of the Dietitians Board Prescriber Training Course – consisting of an online course and a face to face workshop with a summative assessment which demonstrates knowledge to safely prescribe dietetic prescription medicines and knowledge of the regulatory framework for prescribing.

Registered dietitians who prescribe must:

- be in an ongoing supervised prescribing relationship and advise the Board of their supervision arrangements;
- include prescribing and prescribing related developments as part of their continuing professional development; and
- complete the Board's online Annual Prescriber Update on an annual basis.

Registered dietitians authorised to prescribe must present to the Board each registration year, with their application for a practising certificate and evidence that they have maintained their prescribing competence through:

- a practice review of their prescribing;
- successful completion of the online Annual Prescriber Update; and
- ongoing supervision of their prescribing practice by a registered prescriber.

Practice Points PICO 4.1

Dietetic staffing levels should follow the most recent country specific Standards for CF Care[2,3].

CHAPTER 5 NUTRITION ASSESSMENT

T. Crowder & S. King

Significant improvements in the nutritional status of CF populations have been achieved in recent decades. This chapter focuses on the time points, processes and tools for nutrition assessment and guidance on the use of these tools and standards of practice for measurement of nutritional parameters in people with CF.

Disease Aetiology

Suggested nutritional status classification categories are outlined in table 5a. This table will aid identification and prioritisation of higher risk patients for further assessment, and/or nutrition intervention (Chapter 6). Optimal nutritional status may not be achievable for everyone with CF. It is also important ensure that genetic height potential is considered when evaluating nutritional status. Explanations of cut-off values used:

- The Cystic Fibrosis Foundation (CFF) based in the United States of America (USA) have set targets for optimal weight status of a BMI ≥50th percentile for children and adolescents and ≥22 kg/m² (women) and ≥23 kg/m² (men) due to the association between these targets and an FEV_1 >60% predicted. However, it is important to note that this information is derived from population-based cross-sectional data and to date there is no evidence to demonstrate that FEV_1 in an individual can be increased as a result of increasing their BMI or BMI percentile.
- To date there is insufficient evidence to attribute any CF-specific increase in morbidity or health risk to being overweight. There is also no agreed cut-off that defines overweight or obesity in CF. The cross-sectional association between FEV_1 % predicted and BMI in adults shows no further increase in FEV_1 percent predicted for people with a BMI >25 kg/m² and no decline for those with a BMI up to 29 kg/m² [132].

Completing Nutrition Assessments

In order to detect declining nutrition status early on and to optimise outcomes, the following are essential components of a systematic approach to nutrition management:

- Routine and comprehensive nutritional assessments; and
- Comparison to reference standards, previous assessments and nutritional targets for the individual.

Nutrition screening for malnutrition is mandatory for the general population on admission to public hospitals in most Australian states and territories and NZ. As per the Australia and NZ Standards of CF Care, nutrition surveillance by a dietitian is recommended at least four times a year [2,3]. The scope of each review will be dictated by the individual's nutritional needs and priorities.

Recently a number of nutrition risk screening tools for CF have been proposed [246-248]. As yet these tools have not been evaluated for validity in or applicability in the Australian or NZ setting and are not recommended currently. Nutrition assessment tools, including the subjective global assessment (SGA) tool in adults and subjective global nutrition assessment (SGNA) in paediatrics are not typically used as stand-alone nutrition assessment tools for the Australasian CF population. These tools lack the breadth required for comprehensive nutritional assessment in CF and the classification categories are not validated in CF.

A comprehensive nutrition assessment should be undertaken at least annually [2,3]. This should encompass the collection and integration of anthropometric, biochemical, dietary and relevant clinical data, which are compared with previous assessments and clinical status changes; and then used to formulate nutritional goals and a management plan for the individual. While in most cases this occurs on an outpatient basis, there may be circumstances, for example when a patient is unable to travel to an additional clinic appointment, where an annual assessment as an inpatient is justified.

Table 5a. Criteria for weight status in cystic fibrosis*

Nutritional status	Infants <2 years**	Children and Adolescents 2-18 years**	Adults
Optimal	Weight-for-length >50th percentile*** AND weight & length tracking AND within 2 percentile bands of each other	BMI 50-85th percentile using CDC growth chart (Australia)** OR BMI 50-91st percentile using NZ-WHO growth chart**	Female BMI 22-27 kg/m² Male BMI 23-27 kg/m²
Acceptable	Weight-for-length 25-50th percentile AND weight & length tracking AND within 2 percentile bands of each other	BMI 25-50th percentile AND weight & height tracking along previous percentiles AND no recent weight loss	Female BMI 20-22 kg/m² Male BMI 20-23 kg/m² AND no unintentional recent weight loss
Suboptimal – at risk of undernutrition	Weight-for-length 10-25th percentile AND/OR weight or length decreasing >1 percentile band AND/OR no weight gain	BMI 10-25th percentile AND/OR weight loss or plateau over 2-4 months	BMI <20 kg/m² AND/OR ≥5% unintentional weight loss over 2 months
Persistent undernutrition	Persistent weight for length <10th percentile AND/OR weight falling >2 percentile bands with stunting of growth AND/OR failure of previous nutritional interventions to improve nutritional status	BMI <10th percentile AND/OR weight falling >2 percentile bands with stunting of growth AND/OR failure of previous nutritional interventions to improve nutritional status	BMI persistently <18.5 kg/m² AND/OR ≥ 5% unintentional weight loss over 2 months despite previous nutritional interventions, regardless of starting BMI
High BMI	Not applicable **** Use growth chart to identify rapid weight gain.	**Overweight:** BMI 85- 95th percentile using CDC growth chart (Australia)** **OR** BMI >91-98th percentile using NZ-WHO growth chart** **Obese:** BMI>95th percentile using CDC growth chart (Australia)** **OR** BMI>98th percentile using NZ-WHO growth chart** **High risk of developing overweight or obesity** Unintentional weight gain resulting in an increasing of ≥2 BMI centile bands	BMI >27 kg/m² AND/OR unintentional weight gain from previously acceptable BMI of >5 kg within a year.

*Adapted from Australian population guidelines and previous Australasian and international recommendations for CF [1,78,132]

** WHO growth charts are used for all infants < 2 years of age. For 2-18 years, at the time of writing, CDC growth charts are used in Australia, NZ-WHO growth charts are used in New Zealand (http://www.health.govt.nz/our-work/life-stages/child-health/well-child-tamariki-ora-services/growth-charts). Refer to Appendix B for conversion between the two charts.
*** See 'Interpreting anthropometric measurements in children and adolescents' on page 17-18.

**** While there are no evidence-based guidelines for treating overweight in infancy, recognition of rapid weight gain might identify if interventions to ameliorate the rate of weight gain are indicated (Centers for Disease Control, https://www.cdc.gov/mmwr/pdf/rr/rr5909.pdf). Important to distinguish between catch-up growth after early deficit, and rapid weight gain risking overweight or obesity in childhood.

DIET

ANNUAL REVIEW

The annual dietary review should encompass an assessment of diet quality/nutrient density as well as energy and macronutrients. The following should be considered:

- intake (current and recent);
    - Conduct a detailed assessment of energy, macronutrient and micronutrient intake using qualitative and/or quantitative methodology [244,249,250].
    - Quantitative assessment may be more beneficial if nutrition status is of concern. It may also be beneficial when focusing on nutrients most relevant to the patient's nutritional issues and goals e.g. carbohydrate intake and distribution with CF-related diabetes or fat intake for those requiring more tailoring of PERT, iron or calcium to evaluate need for supplementation.
- contribution of alcohol to energy intake (where relevant);
- use of oral/enteral/parenteral nutrition support;
- previous involvement with and/or advice provided by a dietitian;
- the impact of previous dietary advice/education;
- knowledge/beliefs including cultural around food;
- changes in dietary pattern;
- meal time behaviours;
- feeding difficulties;

ROUTINE CLINIC APPOINTMENTS

Routine reviews should identify changes in dietary intake patterns from previous dietetics consultations and include evaluation of changes made in relation to education/advice/goal setting. It should also integrate dietary intake with weight changes/expected weight gain, symptoms (e.g. malabsorption) or biochemical monitoring (e.g. blood glucose levels) as applicable. Any of the considerations listed under annual assessment i.e. use of oral/enteral nutrition support or PERT should also be reviewed, if applicable.

Considerations for infants

- Aim for dietary review with each clinic appointment (usually monthly) until steady growth established and then a minimum of every three months after that.
- An additional dietary review is required around the time of introduction to solids.

Considerations for children (>2 years), adolescents and adults

- Anthropometric parameters are important at each clinic visit which is usually every three months. People with milder genotypes and who are clinically stable from a nutrition and respiratory perspective, a dietary review may only be required six-monthly or annually.

REVIEW DURING ADMISSIONS

In addition to what would be covered during a routine review, the following should be considered in the inpatient setting:

- acute changes in appetite and intake arising from the current reason for admission;
- possible impact of hospital menu/options e.g. refusal to eat hospital food;
- calculation of energy, protein and other relevant nutrient requirements to meet identified nutritional goals of the admission. This is particularly relevant for people receiving enteral nutrition support; and
- quantification of dietary intake in relation to usual intake, calculated requirements and evaluation/integration with weight changes observed in hospital. Methods for assessing dietary intake in hospital include food record charts, mealtime observations and recall methods.
- Frequency of review will vary according to hospital policy and individual patient circumstances.

As a general guide, all people with CF should be seen by a dietitian within 48 hours of admission and a minimum of once per week throughout their admission.

METHODS FOR ASSESSING DIETARY INTAKE

There are a range of methods for assessing dietary intake in CF, including:

- 24 hour recall (qualitative tool that is easily implemented)
- dietary history
- food diaries (3-5 day records)

When choosing a dietary assessment method consider:

- tools and resources available
- timeframe of the assessment (e.g. inpatient short term monitoring of intake vs. annual review)
- specific issues to be assessed
- patient participation and acceptance of the assessment method
- nutritional goals being evaluated or which may emerge from the assessment

Completion of a food diary is necessary for quantitative evaluation of energy and nutrient intake [78]. Moreover, they can be beneficial for completing meal-to-meal analysis (e.g. for carbohydrate counting in CF-related diabetes and evaluation of PERT adequacy). There is a high burden associated with completing food diaries, as well as, a risk of exaggeration of intake. Analysis usually requires a computerised food composition software e.g. *Foodworks®*.

Care should be taken when interpreting results of dietary assessments. In particular, the limitations of the methodology implemented should be considered. For example, multiple day food diaries can result in over- or under-reporting of intake [251].

CLINICAL

- pancreatic status and the efficacy of PERT (Chapter 10);
- relevant medications such as insulin type and timing, fat soluble vitamin regimens and sodium supplementation. Medications directly affecting the gastrointestinal tract may also influence dietary intake e.g. proton pump inhibitors, anti-emetics, laxatives and some antibiotics;
- psychosocial and lifestyle influences that may contribute to dietary intake, and
- other clinical factors that may impact on dietary intake including infection frequency and severity, symptoms affecting dietary intake (e.g. dyspnoea, nausea, vomiting, anorexia, early satiety, reflux, constipation, diarrhoea) and presence of any comorbidities.

ANTHROPOMETRY

Routine measurement of anthropometric parameters is a cornerstone of nutritional status monitoring in CF and plays an important role in the facilitation of early detection of nutritional deficits [249,250,252]. The recommended frequency for routine monitoring of anthropometric measurements is outlined in table 5b.

Routine anthropometric parameters include:

- height (length in those <2 years),
- weight
- BMI (≥ 2 years)

Percent weight loss over time may also be a useful calculation when assessing anthropometric parameters, particularly for adults. During inpatient admissions, weight loss should be compared to 'well' weight and malnutrition status should be documented (Chapter 6).

INTERPRETING ANTHROPOMETRIC MEASUREMENTS IN CHILDREN AND ADOLESCENTS

Plotting a child's growth on a chart contributes to forming an overall clinical impression of that child's nutritional status. However, recommendations regarding choice of growth chart differ between Australia and NZ.

- New Zealand [253]
  - World Health Organisation (WHO) growth chart for the paediatric population (0-18 years)
- Australia [254]
  - WHO growth charts for infants (0-2 years)
  - Centers for Disease Control and Prevention (CDC) growth charts for children and adolescents (2-18 years)

When using the WHO growth standards to measure children 0-24 months, a higher weight-for-length percentile is routinely observed compared to the CDC curves in both the general and CF populations [255,256], meaning that a child who plots above the 50th% percentile weight-for-length on the WHO growth standard between 12-24 months

of age will be below the 50th%ile on transition to the CDC BMI growth curve at 2 years of age. The US CF Foundation recently released a statement recommending a goal of WHO weight-for-length ≥75th percentile for infants aged 12-24 months[257,258] related to the expectation that this will convert to a BMI ≥50th percentile on the CDC growth charts after the age of two years. It is important to note that this is a US recommendation and cannot be automatically generalised to Australia or New Zealand, where newborn screening has been standard practice in CF for over two decades, and infant feeding practices including breastfeeding may differ in both the general and CF populations. It will be prudent to examine and compare such trends using Australian and New Zealand CF registry data before determining whether there is sufficient evidence of better nutritional and pulmonary outcomes for Australia and New Zealand to adopt the US CFF recommendation to aim for a weight-for-length of ≥50th percentile in infants with CF aged 12-24 months.

More information on the use and development of the CDC and WHO growth charts is available via the Royal Children's Hospital Growth Learning Package (http://www.rch.org.au/childgrowth/Child_growth_e-learning/).

Refer to Appendix B for further information on conversion between the two growth charts.

More information on the use and development of the CDC and WHO growth charts is available via the Royal Children's Hospital Growth Learning Package (http://www.rch.org.au/childgrowth/Child_growth_e-learning/)

Additional paediatric specific anthropometric parameters (centile and z-score measures) to consider include:

- head circumference – not routinely measured in infants with CF unless of specific concern
- weight-for-length
- genetic growth potential via mid-parental height
  - Girl's = [(Mother's height + Father's height) ÷ 2] – 7cm
  - Boy's = [(Mother's height + Father's height) ÷ 2] + 7cm

There are many considerations in the practical application of assessing a child's growth. Taking serial measurements is of utmost importance and growth charts are not to be used alone as a nutrition diagnostic tool. Care should be taken when interpreting BMI percentiles for children with poor height growth as falling height percentiles may indicate nutritional stunting. Additionally, parents and caregivers may have difficulty understanding growth charts thus, ongoing explanation and education should be provided.

Table 5b. Recommended frequency for routine monitoring of anthropometric measurements in CF

Measurement	FREQUENCY			Considerations
	Infants	Children and Adolescents	Adults	
Height – supine (length)	Every month until thriving	n/a	n/a	All infant growth charts are based on supine lengths
Height standing	n/a	Every clinic	Annually	When transitioning from length (supine) to height (standing) measurements, there may be a small discrepancy of 1-2cm between methods. 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	Outpatient: weekly until thriving Inpatient: within 24 hours of admission Minimum of once per week On discharge	Outpatient: every clinic Inpatient: within 24 hours of admission	Outpatient: Every clinic Inpatient: within 24 hours of admission	Determine the change in weight status from previous measurement, and compare with goals/targets to identify (as applicable) (a) lack of expected weight gain; (b) weight gain towards a goal; (c) weight gain towards normal growth and development; (d) unplanned weight loss (e) planned weight loss in overweight/obese (f)unplanned weight gain towards overweight/obese range

METHODS FOR ANTHROPOMETRIC MEASUREMENT

Practitioners need to be trained in correct anthropometry procedures and follow standard measurement procedures. This is to ensure appropriate precision and accuracy of measurement so that changes in nutritional status parameters can be detected early and accurately. All centres should have access to a manual of anthropometric procedures and training. Accepted practice standards [1] include:

Infants (<2 years)

- Bare weight 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
- Recumbent length in a supine position on a paediatric measuring board of infants
- Flexible non-stretch tape for measuring head circumference
- Length and weight measurements should be corrected for gestational age in premature infants (i.e. born before 37 weeks gestation) until 2 years of age

Children (≥2 years), adolescents and adults

- Weight measurements taken dressed in light clothing, without shoes and jumper on a platform, electronic chair or beam balance (not bathroom) scale.
- Stadiometer to measure the standing height

Anthropometric equipment should be re-calibrated regularly. All equipment that comes into contact with patients with CF must also be handled and cleaned as per the local "Infection Control" policy for CF.

While BMI and BMI percentiles are most commonly used as indicators of nutritional status, they cannot distinguish if deficits, excess stores or changes in weight are in the fat or fat-free mass (FFM) compartments, or both [213,259,260]. This information, if required, is ascertained via the assessment of body composition which usually encompasses analysis of percent body fat, muscle, water and bone.

There are many body composition assessment methods available, see table 5c for the most commonly used methods. Some of these, however, are not widely available in the clinical setting and are confined to research use only. Newer methods being researched in other disease states include ultrasonography for limb muscle thickness estimation; computerised tomography analysis of skeletal muscle. At the present time, these have not been applied to in CF clinical practice in Australia and NZ.

Where a body composition method yields information on fat-free mass, this can be converted to fat-free mass index (FFMI) by dividing by height-squared (in metres). There are not yet any CF-specific validated cut-offs for FFM or FFMI that correlate with functional status, clinical risk or survival. The recent European Society for Clinical Nutrition and Metabolism (ESPEN) definition of malnutrition in adults proposed a cut-off of FFMI <15kg/m^2 for females and <17kg/m^2 for males [261].

Whilst current evidence does not support the routine assessment of body composition in all individuals with CF, these assessments may be indicated in the following situations:

- Undernutrition, overweight, obesity or unexplained weight gain.
- Assist with nutrition status evaluation, goal setting and evaluation of nutrition interventions after determining if weight changes are reflective of changes in FFM stores, fat stores or both.
- Severe CF lung disease including those being considered for lung transplantation [19].

There is no evidence on which to base recommendations for the frequency of body composition assessment. This should be guided by available resources and individual nutritional goals. If monitoring body composition changes following institution of nutrition support, it is unlikely that clinically important changes in FFM or fat mass would be detectable in less than 1-3 months.

Table 5c. Strengths and consideration of available body composition assessment methods [212,262-266]

	Strengths	Considerations
Skinfold thickness measurements	Quick and non-invasive	Prediction equations for conversion for measurements to FFM and percent fat are based on healthy populations and show variable accuracy in CF
Multi-frequency bioelectrical impedance analysis (BIA) and Bioelectrical impedance spectroscopy (BIS)	Quick and non-invasive Tetrapolar multi-frequency BIA and BIS (newer technology) have fewer limitations than older BIA devices.	Single frequency BIA (older technology) - poor accuracy compared with reference methods • Simple BIA devices such as stand-on scales with only two contact points (feet) are not validated in CF and not recommended as the results may not reflect the distribution of FFM and fat mass across the whole body. • Equipment is expensive to acquire • Limited validation studies in CF with tetrapolar multi-frequency BIA or BIS
Whole body dual-energy X-ray Absorptiometry (DXA) scanning	Accurate reference method for body composition assessment. • Provides information on regional body composition as well as total FFM, fat mass, and bone mineral content. • Newer DXA scanners are much quicker than older devices. • Low exposure to ionising radiation	Whole body DXA scanning is not routinely performed when bone density scanning is undertaken, and may require additional cost. • Requires individual to lie still and flat for duration of scan, which may be difficult for young children and those with severe lung disease.
Mid-arm circumference measurements	Used to assess muscle stores in conjunction with TSF • Simple, quick and non-invasive. • Useful for sequential monitoring	Cannot reliably be converted to whole body FFM stores as arm muscle and fat stores may not reflect whole body distribution
Abdominal circumference	Useful for monitoring abdominal/ central adiposity and comparison with reference norms for metabolic risk in adults with high BMI • Simple, quick and non-invasive. • Measuring abdominal circumference may be useful for identifying excess central adipose tissue in adults with high BMI and for monitoring the effect of interventions in individuals identified as suitable for weight loss.	No CF-specific evidence to determine if the general population cut-offs for abdominal obesity apply to the stratification of risk in this group of adults with CF.
Whole body plethysmography	Has been studied in CF	Not widely available

NUTRITION FOCUSED PHYSICAL FINDINGS

Muscle and subcutaneous fat stores can be visually examined for signs of depletion. Commonly used sites in clinical nutrition are outlined in figure 5a [267].

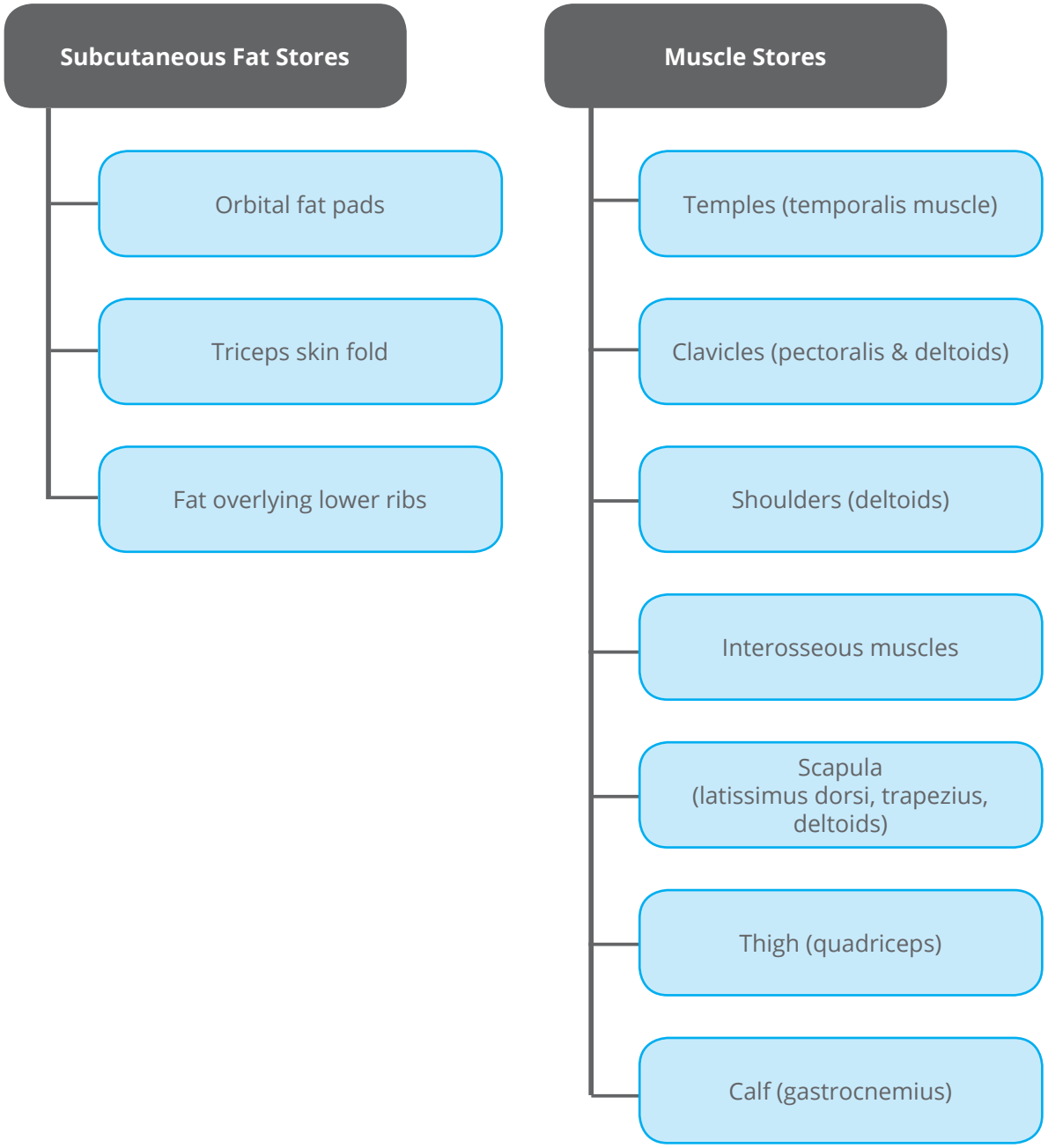

Figure 5a. Sites to assess muscles and subcutaneous fat stores [267]

ESTIMATED ENERGY REQUIREMENTS

Estimation of energy expenditure and thus energy requirements is a key component of the nutrition assessment in CF. The doubly-labelled water method is the gold standard but is extremely expensive and only available in limited research settings. Indirect calorimetry can also be used to estimate energy requirements and is recommended in the general population for those who are malnourished, or critically ill [268,269]. The strengths and considerations of the use of indirect calorimetry are outlined in table 5d.

Table 5d. Strengths and considerations for indirect calorimetry [269-271]

Strengths	Considerations
Measurement of resting energy expenditure (REE) can help identify if energy expenditure is: • Higher than estimated using prediction equations or published targets • Contributing to negative energy balance or failure to meet positive energy balance and nutrition goals	Measurement of REE will not incorporate the following: • Energy cost of physical activity • Energy expended in normal activities of daily living • Additional energy required to offset gut-related energy losses Must be undertaken by trained personnel in accordance with accepted standards and test conditions and local institutional protocols. Not routinely available in all clinical settings, although it may be available in some tertiary hospitals

Overall there are no clinically accessible methods for measuring total energy expenditure. In practice, prediction equations and/or energy targets are most commonly used to evaluate dietary energy intakes and plan targets. Historically, recommendations for energy intake in CF were based on a % of the healthy population RDI values, which were fixed values published for age and gender [272]. Fixed age- and gender-specific RDI values for energy are no longer used as energy targets in Australian or New Zealand nutrition practice for energy targets for the general population [43]. The current approach recommended by the NHMRC should be the basis for calculating energy requirements in CF [43], with adjustment for CF-specific factors.

STEPS TO ESTIMATE ENERGY REQUIREMENTS IN CF

1. Calculate REE (in mJ/day) in using the age- and gender-specific Schofield prediction equation [273]

Age (years)	Male Equation	Female Equation
0-3	(0.249 x weight kg) – 0.127	(0.244 x weight kg) – 0.130
3-10	(0.095 x weight kg) + 2.110	(0.085 x weight kg) + 2.033
10-18	(0.074 x weight kg) + 2.754	(0.056 x weight kg) + 2.898
18-30	(0.063 x weight kg) + 2.896	(0.062 x weight kg) + 2.036
30-60	(0.068 x weight kg) + 3.653	(0.034 x weight kg) + 3.538
> 60	(0.049 x weight kg) + 2.459	(0.038 x weight kg) + 2.755

2. Apply an activity factor based on current physical activity level [273]

Physical activity level	Male	Female
Bed rest	1.2	1.2
Very sedentary	1.3	1.3
Sedentary/maintenance	1.4	1.4
Light	1.5	1.5
Light/moderate	1.7	1.6
Moderate	1.8	1.7
Heavy	2.1	1.8
Very heavy	2.3	2.0

3. Apply a CF-specific stress factor to account for the estimated elevation in energy requirements for that individual, which may encompass energy losses due to malabsorption and/or increased energy expenditure due to CF lung disease. Further information is available in Chapter 7.

Stress factor	
CF	1.1 – 2.0

4. If applicable to the individual's nutrition goals, add or subtract an energy allowance for weight gain or weight loss, to achieve positive or negative energy balance respectively [274].

Prediction equations typically use total body weight as a variable, however, the major variables influencing resting energy expenditure are FFM and disease state [268]. In situations where FFM is outside the general population reference range, as is often the case in CF, prediction equations may yield greater inaccuracies. In CF, both low percentage body fat (high FFM) and depleted FFM can occur [213,225]. This may result in under- and over-estimation of resting energy expenditure (REE) [43,274,275]. It is important to note that if REE is elevated, total energy expenditure (TEE) is not necessarily higher for people with CF. This is thought to be due to lower physical activity that offsets the effects of higher REE [276].

There are no evidence-based recommendations to guide practice around the frequency of revising estimated energy requirements for a person with CF. Practitioners should consider the clinical application and benefits of calculating energy requirements as frequent calculation of requirements without quantifying intake, may not be relevant to practice. Situations in which calculating a revised energy requirement may be important include:

- review of an infants or young child during a period of rapid growth (particularly important for children with faltering growth);
- during hospital admissions where energy requirements are likely to fluctuate (especially at the beginning of admission if acutely unwell and when activity levels may be lower than usual);
    - This is particular important for those requiring enteral nutrition support
- when instituting and evaluating a nutritional intervention aimed at improving weight status;
- when instituting and evaluating a nutritional intervention aimed at reducing weight in overweight/obese;
- when exercise/activity has changed; and
- during pregnancy/lactation.

BIOCHEMCAL & LABORATORY DATA

There are no specific biochemical parameters that indicate nutritional status in isolation from other nutritional assessments [277]. Serum albumin is not a useful marker of nutritional status or protein intake in acute or chronic illnesses associated with infection and/or inflammation. Even during periods of apparent clinical stability, a high proportion of adults with CF have serum albumin below the reference range despite adequate protein intakes [262] which is likely to reflect chronic infection and inflammation rather than protein intake or nutritional status.

Care should be taken with interpretation of nutritional biochemistry during acute illness. While it may appear convenient to undertake periodic measurement of markers of micronutrient status during a hospital admission, many markers are affected by the acute phase response which occurs during acute illness. Chapter 8 and Chapter 9 discuss these topics in further detail.

Monitoring and Evaluation

The components of nutrition assessment for CF, as outlined above, are also those which are used for the monitoring and evaluation of nutrition status and care. The results obtained from routine assessments and reviews may trigger escalation to more detailed and focused assessments.

A systematic approach to nutritional monitoring/review, together with comparison with reference standards, previous assessments and nutritional targets for the individual, are essential to optimise nutrition outcomes and detect any decline in nutrition status over time.

The following sub-groups of people with CF are more likely to require more intensive monitoring and review:

- infants and young children during periods of rapid growth
- those at risk of or who have persistent undernutrition or overweight/obesity
- those requiring oral, enteral and parenteral nutrition support
- women who are pregnant or lactating
- those with known CF co-morbidities

CHAPTER 6 NUTRITION INTERVENTIONS

N. Forgione, N. Saxby, S. King, R. Cavanagh & T. Crowder

The historical focus of nutrition interventions for people with CF has centred on managing undernutrition [1]. Today, practitioners are also faced with the emerging issue of overweight and obesity amongst the CF population [199,278]. This chapter provides guidance for nutrition interventions based on the nutritional status categories as outlined in Chapter 5 (see table 5a). Table 6a below shows recommended escalation of routine care that should be considered due to the risk of development of undernutrition or overweight and obesity.

Table 6a. Recommended nutrition intervention strategies based on nutrition status category

Nutrition status category	Recommendations for nutrition intervention
Optimal	Routine nutritional care and surveillance +/- education and preventative counselling
Acceptable	Routine nutritional care and surveillance +/- education and preventative counselling
Suboptimal: at risk of undernutrition	Nutritional counselling, behavioural management +/- oral nutrition supplements
Persistent undernutrition	As above, plus medical +/- psychological evaluation investigating factors contributing to undernutrition. Consider intensive nutritional support via enteral nutrition
High BMI : at possible risk related to overweight or obesity	Diet and activity assessment, plus consideration of medical and psychosocial contributing factors. Consider goal-directed nutritional counselling[7]

6.1 Undernutrition

Despite rapid and continuous advances in CF treatments, suboptimal nutritional status amongst people with CF remains common [188]. According to the 2014 Australian Cystic Fibrosis Data Registry report, between 2 to 11 percent of adults with CF have a BMI of less than 18.5 kg/m^2 (i.e. the International Classification of Diseases (ICD 10) criterion for malnutrition [188]). Adult females are almost three times more likely to be undernourished than their male counterparts [188]. Undernutrition can be present from birth and the Australian CF Data Registry reports 6.6% of children with CF have a BMI less than the 10th percentile [188].

Disease Aetiology

The drivers of undernutrition in CF are complex and multifactorial. They include:

- Increased resting energy expenditure which may arise from a combination of:
  - lung infection and inflammation (through oxidant injury and inflammatory mediators) [224,227]
  - increased work of breathing and coughing [279]
  - acute respiratory exacerbations which cause transient periods of increased resting energy expenditure (REE) in many patients [223,224,228]
- Decreased protein synthesis [280]
  - associated with a systemic inflammatory response, more severe pulmonary disease and nutritional deficits [223,224,228]
- Reduced absorption of nutrients:
  - pancreatic insufficiency results in maldigestion and subsequent malabsorption of macronutrients [78], which is partially (although not completely) overcome with pancreatic enzyme replacement therapy (PERT)

  - inadequate dosing or timing of PERT results in missed opportunities for optimisation of fat absorption [202]
  - other conditions which have the potential to compound malabsorption are: CF-related liver disease, DIOS, short gut syndrome, intestinal inflammation, low bicarbonate output, delayed gastric emptying rate and small intestinal bacterial overgrowth [202]

- Increased energy losses and metabolic alterations:
  - vomiting precipitated by coughing [1]
  - CF-related diabetes (particularly that which is poorly controlled), impaired insulin secretion and insulin resistance results in hyperglycaemia and glycosuria [78]
- Inadequate dietary intake:
  - anorexia resulting from illness or symptoms such as bloating, nausea or GOR can impede the individual's ability to consume adequate amounts [1]
  - inflammation may contribute to decreased appetite due to the release of cytokines by immuno-competent cells, particularly during pulmonary exacerbations where inflammation increases and appetite is suppressed. (This can improve following antibiotic treatment) [281,282]
  - altered body image and dysmorphia may limit the desire to maintain a sufficient nutritional intake [283]
  - psycho-social issues, low mood, treatment burden and a lack of general well-being may mean the effort required to consume a nutritionally adequate diet is more difficult for some [78]
  - children and infants may experience feeding problems, meal time behaviours or interactions with parents that challenge the achievement of adequate nutritional intake [4,5,8-10]

It is also known that lung transplantation (Chapter 16) and pregnancy (Chapter 14) in CF place further stress on diet and nutritional status [1,190.]

Assessment of undernutrition

As the differential diagnosis for undernutrition in CF is broad, it is important that the wider CF treating team (nurse, respiratory physician, gastroenterologist, endocrinologist, psychologist, social worker, physiotherapist) assist in exploring the multi-faceted nature of undernutrition [202]. The specific nutrition expertise of the CF dietitian places them in the ideal position to lead a coordinated assessment approach.

DIET

In people with undernutrition, pay particular attention to:

- total energy intake:
  - energy, protein, fat and caloric density of foods
  - use of supplementary nutritional support
  - fat intake at each meal compared to dosing of PERT
- frequency of meals and snacks
- food and nutrition related knowledge and beliefs
- mealtime behaviors and environment
- food security and preparation skills
- energy demands of illness and exercise
- adherence to and impact of previous nutrition intervention

CLINICAL

GENERAL CONSIDERATIONS

- review an individual's lung function status and trends
- monitor pulmonary symptoms and frequency of respiratory exacerbations
- consider screening for the presence of, and review control of, comorbidities that may contribute to undernutrition:
  - **gastrointestinal system** (Chapter 11). Inadequately treated pancreatic insufficiency, constipation, motility issues (including delayed gastric emptying), small bowel bacterial overgrowth, GOR, irritable bowel syndrome and fermentable carbohydrate malabsorption, CF-related liver disease and coeliac disease

  - **endocrine system** (Chapter 12). CF-related diabetes and lesser degrees of altered glucose metabolism, hypothyroidism, growth hormone deficiency, menstrual cycles and gonadotrophin deficiency secondary to low body weight. In females luteinising hormone (LH) and frolics-stimulating hormone (FSH) and testosterone blood levels
- consider the impact of anxiety, depression, stress, eating disorders, body dysmorphia or other behaviours on a person's ability to achieve adequate nutrition
- check available support systems (family, partner, friends, community links)

ANTHROPOMETRY

Routine anthropometric parameters include:
- height (length in infants <2 years),
- weight, and
- BMI.

It is also important to consider genetic growth potential in children and adults using the mid-parental height technique (Chapter 5).

BODY COMPOSITION

Body composition assessment may augment anthropometric data to identify the presence of depleted fat free mess (FFM) stores, fat stores or both [78,213,225] (Chapter 5).

PHYSICAL ASSESSMENT

Visually examine muscle and subcutaneous fat stores for signs of depletion (Chapter 5). While signs of oedema are not specific to undernutrition, they are useful to note as oedema may mask the true extent of weight loss. [267]

BIOCHEMICAL AND LABORATORY DATA

There are no specific biochemical tests that indicate or validate the presence of undernutrition. General laboratory tests (e.g. routine measuring of urea, electrolytes and fat soluble vitamin levels, liver function tests and inflammatory markers) may contribute to characterising undernutrition and identifying contributing co-morbidities [78].

Nutrition Diagnosis

MEDICAL DIAGNOSTIC CRITERIA AND DOCUMENTATION OF MALNUTRITION

Malnutrition is a more formal classification of undernutrition encompassing specific clinical, anthropometric and physical criteria in children and adults. There is considerable work currently in progress at an international level in the general clinical nutrition field to define malnutrition and related nutrition disorders including cachexia and sarcopaenia [261,267].

An international working party is currently developing an international standard for defining malnutrition that will likely inform the next round of disease classifications (i.e. ICD-11). These definitions are important because they drive coding and thus influence hospital reimbursement. Some individuals with CF with undernutrition requiring intervention are likely to meet the generic clinical and coding criteria for the diagnosis of malnutrition.

Until the release of ICD-11, malnutrition status should continue to be documented for clinical coding where this is part of institutional requirements.

- adult malnutrition coding criteria: BMI <18.5 kg/m^2 and/or unintentional weight loss > 5% with evidence of suboptimal intake resulting in loss of subcutaneous fat and/or muscle wasting [284]
- paediatric malnutrition coding criteria [284]
  - Mild malnutrition BMI z-score -1 to -2
  - Moderate malnutrition BMI z-score -2 to -3
  - Severe malnutrition BMI z-score ≤-3

Intervention

It is important to realistically assess an individual's acceptance and commitment to any potential nutritional interventions, including review of the impact of previous nutrition interventions.

ROUTINE NUTRITION EDUCATION AND PREVENTIVE COUNSELLING

As energy requirements will vary throughout life stages and with disease progression, it is likely that a high protein, energy and fat diet may be required to assist in maintaining nutritional status in people with CF [285]. Nutritional education to promote optimal weight status should be provided throughout the lifespan of those with CF. In order to achieve elevated nutrition requirements in the context of the daily diet, high protein and energy diet strategies are common practice in the nutritional management of CF [202].

This may include [249]:

- the inclusion of high protein foods at each meal
- encouraging the consumption of energy dense foods, particularly those that are also nutrient dense
- the fortification of foods with additional sources energy
- encouraging frequent meals or the addition snacks in between meals, and
- the consumption of drinks naturally high in protein or energy to supplement intake outside of meal times

During periods of illness, progressing CF lung disease or malnutrition, dietary intervention strategies may need to be intensified and increased. This may require additional support, re-enforcement of strategies and perhaps the progression to commercial nutritional supplements [249]. Similarly, during exacerbations requiring inpatient hospital admission, the CF dietitian should ensure the provision of a nutritionally sufficient hospital diet. This may require higher protein or energy items to be offered to CF patients above and beyond the usual hospital menu items and depending on nutritional risk, may progress on to commercial oral or enteral supplement provision.

BEHAVIOURAL MODIFICATION STRATEGIES

The literature regarding behavioural modification strategies around food and mealtimes for people with CF is currently limited to children.

Compared to standard nutritional care, do behavioural interventions around food and mealtimes improve behaviours, diet variety, and weight or nutrition status in children with CF? PICO 6.1.1

[Grade B] Offer behavioural modification strategies to children at risk of/or with identified undernutrition. Conduct behavioural modification strategies in combination with nutrition education. [4-8]

Behaviour modification strategies are a valuable component of standard paediatric CF care, especially for children with or at risk of undernutrition [4-8]. The following behaviour modification strategies have been found to be effective:

- differential attention (praise and ignoring),
- contingency management (child only receives a desired reward after they have eaten their meal and/or performed desired mealtime behaviours), and
- self-monitoring of food intake (parents and/or child) and parental limit setting (establishing clear expectations and consequences).

It has been shown that the best results are achieved when behavioural strategies are conducted in combination with nutrition education [5,8,10].

When should behavioural interventions around food and mealtimes be considered for children with CF? PICO 6.1.2

[Grade C] Commence behavioural modification strategies early in life (i.e. during infancy or toddlerhood) and potentially continue throughout childhood. Offer the following strategies:

- Differential attention (praise and ignoring)
- Contingency management (child only receives a desired reward after they have eaten their meal and/or performed desired mealtime behaviours)
- Self-monitoring of food intake (parents and/or child)
- Parental limit setting (establishing clear expectations and consequences) [7,9,10]

Research indicates that behaviour modification strategies are to be considered at a young age, before disruptive eating and mealtime behaviours become an ongoing issue. There is also evidence to support the ongoing use of these strategies throughout childhood [7,9,10].

The Behavioral Pediatrics Feeding Assessment Scale (BPFAS) is a validated questionnaire for children aged 7 months to 7 years that has been used to assess the frequency of child and parent behaviours during mealtimes [286]. This tool has been used successfully with the CF population [287].

Easy to implement behavioural management strategies include [4-8]:

- normalise food and eating by making mealtimes enjoyable experiences;
- encourage a structured approach to meal and snack times;
- set rules and clear expectations for desired behaviours (e.g. limit meal times to 15 minutes for toddlers, 20 minutes for young children);
- set energy goals for meals and snacks;
- encourage new foods;
- praise child for eating, and complement appropriate eating behaviours (e.g. verbal "nice job with eating everything on your plate, non-verbal high five, hug);
- ignore child complaints or disruptive behaviors incompatible with eating (e.g. turn away from child, leave the room, silence, get up from the table);
- remove distractions at mealtimes (e.g. television, computers, electronic tablets, toys);
- provide extra fluids only after a meal is eaten; and
- provide regular reward incentives for meeting caloric goals (e.g. star charts, trophies)

Many paediatric hospitals have practice guides and education resources to help clinicians further explore the use behavioural modification strategies in their practice.

APPETITE STIMULANTS AND GROWTH HORMONE

The use of appetite stimulants to improve nutritional status in CF is limited due to concern over adverse side effects and insufficient evidence to support routine use in patients with CF.

Megesterol acetate was first used to treat breast cancer and is chemically similar to progesterone [288]. One of its side effects is stimulation of appetite. The exact mechanism as to how megesterol acetate stimulates appetite is not known [289]. It is proposed that it may have an effect on the inflammatory process (cytokines) whereby lowering cytokine levels have been shown to have an effect on the treatment of anorexia and cachexia in patients with cancer [290,291].

Cyproheptaine (Periactin®) is an anti-histamine that has a secondary effect of stimulating appetite. Its mechanism for stimulating appetite is not known however it is thought to interfere with serotonin levels [292,293].

Do appetite stimulants, megesterol acetate and cyproheptadine, improve nutritional status in CF? PICO 6.1.3

[Grade C] There is some evidence to suggest that appetite stimulants may improve weight and appetite for people with CF. However, the potential risk of adverse side effects and insufficient evidence means that routine use of appetite stimulants to improve nutritional status is not recommended. [11]

The 2014 Cochrane systematic review regarding the use of appetite stimulants in CF included three small randomised and quasi-randomised controlled trials (n=47 patients total) that look specifically at the use of megesterol acetate and cyproheptadine hydrochloride in CF [11]. The results of the meta-analyses found that [11]:

- weight z-score significantly improved across all trials after 3 months of use
- weight significantly improved after 6 months with megesterol acetate use in one study
- no significant impact on pulmonary outcomes (FEV_1 percent predicted)
- a statistically significant increase in the proportion of patients with an increased appetite.

Despite the potential for appetite stimulants to improve weight and appetite in the short term (6 months), there is inadequate evidence to support their use in CF at this point in time [11]. There is also concern regarding their safety as potential adverse side effects of appetite stimulants use are not well documented [11]. Potential side effects of appetite stimulants include [11]:

- impaired blood glucose control
- fatigue
- mood
- fluid retention
- shortness of breath
- elevated liver transaminases.

Growth hormone is an anabolic agent that promotes the synthesis of protein, optimises fat utilisation and reduces the oxidation of glucose.

Does the use of recombinant growth hormone improve nutritional status in pre-pubertal people with CF? PICO 6.1.4

[Grade C] There is some evidence to suggest that growth hormone may improve height, weight and lean tissue mass for pre-pubertal people with CF. Routine use of growth hormone to improve nutritional status in people with CF is not recommended. [12]

The 2015 Cochrane systematic review regarding the use of recombinant growth hormone therapy in CF includes 4 randomised and quasi-randomised controlled trials (n=161 patients total, study durations 6-12 months). The review specifically focuses on the use of growth hormone therapy on lung function, quality of life and clinical outcomes in children and young adults [12]. The results of the meta-analyses found that growth hormone use [12]:

- Modestly improves height, weight and lean tissue mass;
- Improvement in lean tissue mass;
- Has no consistent impact on lung function, muscle strength, clinical condition and/or quality of life; and
- Has no effect on glucose metabolism and doesn't increase the chance of developing CF-related diabetes.

ORAL NUTRITIONAL SUPPLEMENTS

Is there any rationale for the use of commercial oral nutritional supplements in addition to food and mealtime strategies to improve nutritional intake, weight or pulmonary function in CF? PICO 6.1.5

[Grade B] Consider the use of oral nutrition supplements on an individual basis. There is no clear evidence that their routine use in addition to food and behavioural modification strategies will result in improvements to nutritional intake, weight or pulmonary function in CF. [13-19]

Oral nutrition supplements (ONS) are unlikely to result in improvement in outcomes such as BMI, nutritional intake or pulmonary function in adults and children with CF over and above the use of routine dietary advice and monitoring alone [13,14,16-19,249].

ONS may replace some of the energy taken as food and their potential effect on overall total energy intake may be either reduced or eliminated. This does not mean that these products may not be efficacious in some individuals, but that clinicians should balance potential benefits against potential adverse effects [14]. ONS should not be regarded as essential in the long term care of all individuals with CF who are malnourished [13,14,249]. Further randomised controlled trials are needed to establish the role of short-term ONS in people with CF and acute weight loss and also for the long-term nutritional management of individuals advanced lung disease [249].

If it is thought that ONS may aid in achieving nutritional adequacy, the choice of supplement should be assessed on an individual basis dependent on the patient's nutritional requirements, age and taste preferences. At the commencement of ONS, clear and measurable outcomes should be set to assist in evaluating effectiveness. This can guide the need for continuation, reduction or cessation of ONS depending on whether outcomes are met. ONS should complement the normal food intake and are best taken after a meal or in between meals and snacks so as not to replace the appetite for normal food [78].

There is a wide variety of ONS available on the market. They commonly come in the form of milk or fruit flavoured drinks, custards, puddings, protein bars and macronutrient powders or liquids. They contain energy ranging from 4.2-8.4kJ/ml (1-2cal/ml), additional protein from whey or plant sources and are sometimes fortified with vitamins and minerals.

ENTERAL FEEDING

Enteral tube feeding may be considered in undernourished patients or those with declining nutritional status where oral nutrition support interventions have proven insufficient to meet nutritional goals. However, it should be noted that the quality of the evidence base for the use of enteral feeding in CF is poor; hence outcomes may vary on an individual basis in the clinical setting. The decision to place an enteral feeding tube should be made on a case-by-case basis.

Should enteral feeding be considered to improve nutrition outcomes for people with CF? PICO 6.1.6

[Grade B] Consider enteral feeding as a means of improving markers of weight, BMI and BMI z- score in adults and children with CF who have been assessed as being undernourished. [20-29]

Should enteral feeding be considered to improve pulmonary status in people with CF? PICO 6.1.7

[Grade C] Practitioners should refrain from commencing supplementary enteral feeding for the sole purpose of improving or stabilizing pulmonary outcomes. [20-26,28]

Practitioners should expect the most favourable nutritional gains to take place in the first six to 12 months of enteral tube feeding [20-29]. However, poor compliance with feeding regimens, CF-related diabetes, and young age at tube insertion may not predict success of nutritional rehabilitation with enteral feeding [21]. In regards to the effect of enteral tube feeding on pulmonary outcomes, there is weak and inconsistent evidence that enteral feeding helps to improve pulmonary function or stability [20-26,28].

When should enteral feeding be introduced for people with CF? PICO 6.1.8

[Ungraded] There is insufficient evidence to make a recommendation regarding when to introduce enteral nutrition in CF. Evaluate appropriate timing on an individual basis.

Despite the lack of conclusive evidence, it is suggested that gastrostomy feeding should be used earlier to optimise growth in CF children. In adults, enteral feeding is likely to be more successful if initiated before advanced lung disease is irreversibly established [25,27]. Aggressive nutrition support by way of tube feeding should be planned [21]. Practitioners should aim to optimise pulmonary status prior to gastrostomy insertion [294].

What is the ideal enteral feeding regimen for people with CF? PICO 6.1.9

[Ungraded] There is insufficient literature to suggest the ideal enteral formula or regimen in the CF population. Select enteral formulas and devise enteral feeding regimens on an individual basis.

What are the risks associated with enteral feeding in CF compared to the general population? PICO 6.1.10

[Grade C] People with CF are not at increased risk of major complications and mortality as a result of enteral feeding. Minor side effects of enteral feeds, including stoma site issues and GOR should be managed as for the general population.

Enteral feeding in CF is safe, including in people with low lung function and in those prone to pulmonary exacerbation. No major complications or mortality have been reported in the literature. Studies describe a range of minor complications associated with enteral feeding in CF, such as stoma site issues and GOR. Minor complications may not warrant the cessation of feeding, instead requiring change in feeding management or a non-invasive treatment [20-27,29]. Documented risks associated with enteral feeding in CF include:

- Gastrostomy site, itchiness, redness and infection [24]:
  - Regular stoma monitoring and Involvement of a gastrostomy credentialed dietitian or stoma specialist nurse may help in preventative treatments for local site irritation [132];
- Increasing symptoms of GOR:
  - May result in less favourable nutritional outcomes if not symptomatically controlled [27]. Positioning at a 30-45% angle during feeding [295]. A slower feed rate and post pyloric feeding may be of assistance in GOR [1].
- Bloating or nausea during enteral feeds:
  - May benefit from the use of prokinetic or antiemetic agents pre feed [132]
  - Review PERT dosing strategies as outlined in chapter 10.
- Increased incidence of hyperglycaemia or CF-related diabetes [22]:

- Review CF-related diabetes management prior to tube insertion [294].
- Pre, mid-way and post feeding blood glucose monitoring is indicated when enteral tube feeding is commenced [29].
- A small dose of insulin pre feeding may be required in some cases [78].

In 2016, the Cystic Fibrosis Foundation (CFF) released evidence-informed guidelines for enteral tube feeding individuals with CF. These guidelines are based on a thorough review and critique of 241 papers addressing a number of PICO questions specifically relating to enteral tube feeding in CF [294]. A total of 33 recommendations, all with 100% agreement, were established by an interdisciplinary working group [294]. This may be an additional useful reference for clinicians exploring enteral feeding. These American guidelines are compatible with the recommendations within this chapter.

Considerations for nutrition support funding:

- Facilities around Australian and NZ have varying centre-based protocols for the provision and funding of oral and enteral supplements and equipment to people with CF.
- Many Australian states are able to provide patients with hospital funded enteral and/or oral formula and supplies. However, in some states, and the private sector, people with CF may be required to fund their own products.
- In NZ all enteral feeds and equipment are supplied at no cost to the patient and ONS are either fully or partly subsidized by PHARMAC[1*].

PARENTERAL NUTRITION

Parenteral nutrition is not recommended for routine use or long-term treatment in CF due to the requirement for centrally placed catheters, the risk of complications (including line sepsis and new onset diabetes) and the challenges associated with administering parenteral nutrition outside the hospital setting. However, parenteral nutrition may be useful for short term support during bowel obstruction, meconium ileus, major gastrointestinal surgery and in the severely ill person with CF awaiting lung or liver transplantation [279]. The initiation, management and monitoring of parenteral nutrition should be guided by the specialist interdisciplinary team, hospital protocols and evidence-based parenteral nutrition guidelines.

Monitoring & Evaluation

People with CF who are taking ONS or enteral feeding should be reviewed regularly to assess tolerance, adherence, progress towards objectives and ongoing need [1]. It is important to monitor for disordered eating, oral intake aversion and other behavioural concerns in adults and children [294].

Enteral feeding could be withdrawn at any time deemed necessary or appropriate by the individual with CF or the treating team. If goals of feeding are met, the individual is nutritionally stable and the gastrostomy is not likely to be required again in the near future consideration could be given to its removal. Similarly, if the tube is inhibiting quality of life or psychosocial health and nutritional goals are not being met, removal of feeding tubes should be considered.

Practice Points PICO 6.1.1 & 6.1.2

Behavioural modification strategies are a valuable component of standard paediatric CF care

Strategies should be considered at a young age, before disruptive eating and mealtime behaviours become an ongoing issue.

For best results, strategies should be conducted with nutrition education.

1 *PHARMAC (Pharmaceutical Management Agency) is the NZ Crown agency that decides on which medicines are subsidised for use in the community and public hospitals.

Practice Points PICO 6.1.3 & 6.1.4

The decision to commence an appetite stimulant should made as an interdisciplinary team and in consultation with the individual with CF and their family or carers, following evaluation of potential benefits and risks in the individual with CF.

The most commonly used appetite stimulants in CF are megesterol acetate and cyproheptadine (periactin).

- They may improve weight and appetite but evidence is inconclusive.
- Some concerns regarding side effects and therefore safety with longer term use.

Growth hormone may improve height, weight and lean tissue mass for pre-pubertal individuals with CF, however, longer term randomized controlled trials are required.

- Until more studies are done looking at the longer term use of growth hormone, it is not recommended for routine use CF

Prior to commencing a trial of appetite stimulants in CF, issues to explore include:

- Identification of other factors that may be contributing to a poor appetite and subsequently poor weight gain or growth and where possible, treat the underlying cause first.

Practice Points PICO 6.1.5

Where possible, avoid using oral supplements as a meal substitution

- Oral supplements should complement usual intake
- Best taken after a meal or as a snack
- A maximum of three oral supplements daily is often recommended to avoid a reduction in appetite around mealtimes.
- Particularly important for the paediatric population where normalised eating is still developing.

Regularly review oral supplement tolerance, adherence and nutritional status response.

The most commonly used oral supplements in CF are dairy based and usually 1-1.5kcal/ml.

Evaluate individual cost versus benefit because oral supplements can be a financial burden because funding for nutrition support varies across the health systems in Australia and New Zealand.

Practice Points PICO 6.1.6 & 6.1.7

The decision to commence either short or long term enteral nutrition support should be made by an interdisciplinary team and in consultation with the individual and their family, including discussion of risks and benefits.

- Benefits on nutrition outcomes, particularly weight and BMI are well documented
- There is no conclusive evidence to support beneficial effects on pulmonary function

The decision can be emotionally challenging for some people with CF. Where possible, appropriate psychosocial support should be provided and the individual's decision should be respected**.** An anaesthestist should be consulted prior to surgical or endoscopic gastrostomy tube insertion in people with moderate to severe CF lung disease.

Practice Points PICO 6.1.8

No evidence to support best timing for enteral nutrition support in CF. The following considerations should be noted in regards to timing of enteral nutrition:

- The person is unable to meet nutritional requirements via oral intake alone
- Conduct Interdisciplinary review with investigation of reasons for any decline in nutrition status and interventions commenced as appropriate
- Explore the role for behavioural modification strategies (In the paediatric population)
- Whilst many patients will have had a trial of oral nutritional supplements (ONS) prior to the need for enteral nutrition being assessed, there is no evidence that favours assessing the impact of ONS first, over proceeding to enteral nutrition. Evaluate whether to trial ONS prior to considering enteral nutrition on an individual basis

Enteral nutrition should be commenced prior to the onset of significant disease progression and FEV_1 decline for more favourable nutritional outcomes

Practice Points PICO 6.1.9

Enteral feed regimens should be devised on an individual basis

The following considerations should be assessed in relation to the individual:

- Caloric targets should be calculated by the specialist dietitian.
- Overnight continuous feeds are usually recommended to preserve appetite and oral intake during the day, though supplementary bolus feeds may also be useful for some people.
- Feed composition
- The choice between polymeric, semi-elemental and elemental feeds should be made on an individual basis.
- Many people with CF will tolerate polymeric feeds well and more specialised formulas are not usually required.
- Choose energy dense feeds i.e. 1.5-2kcal/ml where possible
- Evaluate individual cost/financial burden versus benefit because funding for enteral nutrition varies across the health systems in Australia and New Zealand.
- Feed tolerance should be reviewed regularly
- Co-morbidities such as reflux may play a role in feed regimens and enzyme dosing strategies (Chapter 10).
- Feeding route
- Nasogastric feeding is usually recommended when feeds are required for < 3 months.
- Gastrostomy insertion should be considered when feeds are required for > 3 months.

For supplementary feeding, aim to meet 30-60% of the individual's calculated energy requirements, or to meet a specifically calculated energy deficit in the diet.

Practice Points PICO 6.1.10

Enteral feeds are considered safe for the CF population. However, as with any intervention, potential risk factors should be evaluated and investigated prior to feed commencement. Safety considerations around enteral feeding include, but are not limited to the following:

- Nasogastric tubes
- Insertion may be difficult and uncomfortable for people with nasal polyps
- Tubes may be dislodged with significant coughing and/or vomiting
- Gastrostomy tubes
    - Aim to optimise pulmonary to health prior to placement of gastrostomy tube
    - Plan for postoperative pain management with the goal of initiating airway clearance within 24hrs
    - Gastrostomy site, itchiness, redness and infection are common. Regular stoma monitoring is recommended.
- GOR
    - Positioning: ensure the person is elevated to a 30-45% angle during feeding, reducing feed rate and post pyloric feeding may be of assistance
- Bloating or nausea during enteral feeds may benefit from the use of prokinetic or antiemetic agents prior to feeding.
- Potential risk of hyperglycaemia or CF-related diabetes. Blood glucose monitoring is indicated prior to, mid-way through and at the end of feeding.

Dietetic department protocols should guide the use of gastrostomy tube and care education prior to discharge home with a feeding tube.

6.2 Overweight and Obesity

N. Saxby, T. Crowder, N. Forgione & S. King

Recent data from around the world show that the proportion of people with CF who are overweight/obese is increasing [199,278,296]. In one study, based at an American CF centre, it was identified that 23% of children and adolescents with CF had an average BMI percentile greater than 90 [278]. Similar rates of overweight and obesity BMI were identified among a Canadian adult CF population in 2011 [199]. Overweight/obese individuals (all ages) with CF tended to be older, have better lung functions, have milder genotypes, and were more often male and pancreatic sufficient [199].

Whilst the significance of overweight and obesity in people with CF is unknown, recent research suggests that coronary artery disease, hypertension and obstructive sleep apnoea area emerging areas of concern for this sub-population group [278]. There also appears to be minimal benefit to lung function when adults with CF have a BMI greater than 25 kg/m^2 and thus a high BMI needs to be balanced against the known health risks of obesity [199].

Disease Aetiology

Overweight and obesity can be attributed, at least in part, to continuously advancing treatment options for CF (e.g. genetic modulator therapies), longer life expectancies, and increased prevalence of obesity in the general population [190]. There is no research, as yet, into metabolic risks of excess adiposity in CF. However, with increased longevity, people with CF may potentially be at risk of some of the metabolic complications seen in the general population.

Assessment

DIET

Attention should be given to:

- Total energy intake and nutrient density of foods; and
- Diet quality to ensure that micronutrient requirements are being met.

CLINICAL

GENERAL CONSIDERATIONS

- Lung function, stage of disease and goals of care
- Assess a person's willingness to make the behavioural changes needed to maintain and/or lose weight (readiness for change)
- Psychological issues associated with weight (especially in younger women)
- Lung transplant - some lung transplant centres accept people with a BMI up to 29 kg/m^2 while others have a lower cut-off
- The risks of metabolic disease (eg type 2 diabetes, cardiovascular disease) should be considered particularly in those with mild lung disease and who are over the age of 30 years. Diagnosing metabolic disease/s, however, is particularly challenging in CF.

ANTHROPOMETRY AND BODY COMPOSITION CONSIDERATIONS FOR OVERWEIGHT/OBESE INDIVIDUALS

- Measuring abdominal circumference may be useful for identifying excess central adipose tissue in adults and for monitoring the effect of interventions in individuals identified as suitable for weight loss. As yet there is no CF-specific evidence to determine if the general population cut-offs for abdominal obesity apply to stratification of risk for people with CF.
- Other body composition measurement techniques may be useful to assess relative contribution of FFM (especially in males)

Table 6c. Summary of anthropometric criteria to diagnosis of overweight and obesity in CF*

	Classification criteria - High BMI - at possible risk related to overweight and obesity
Infants	n/a
Children & Adolescents	**Overweight:** BMI 85-95th percentile if using CDC growth chart (Australia) **OR** BMI 91-98th percentile if using NZ-WHO growth chart **Obese:** BMI >95th percentile if using CDC growth chart (Australia) **OR** BMI >98th percentile if using NZ-WHO growth chart **High risk of developing overweight or obesity** Unintentional weight gain from previously acceptable BMI percentile: gain of more than 2 BMI percentile bands
Adults	BMI >27kg/m^2 **OR** Unintentional weight gain from previously acceptable BMI of >5kg within one year

* Refer to table 5a for more information

Intervention

There is a lack of evidence available to substantiate interventions for the management of overweight and obesity in people with CF. Leveraging the recommendations for the general population, when appropriate, can provide some guidance to practitioners. It is important to note however, that general population recommendations are intended for use in people with stable health, milder genotypes and good lung function and thus they may not always be appropriate for the CF population. In adults with severe CF lung disease and a BMI>27kg/m^2, achieving reduction in fat mass while preserving lean mass is likely to be challenging. In such individuals, who may have limited exercise capacity, intentional or unintentional weight loss is likely to be predominantly lean mass. This may be associated with reductions in strength and function. Advice regarding nutritional status and metabolic risks should take into account body composition and include monitoring for signs of sarcopaenic obesity and potentially increased mortality [297] .

For people with CF consider the appropriateness of the current clinical practice guidelines for the management of overweight and obesity in children, adolescents and adults in Australia [298] and NZ [299,300].

Advise people about the potential health benefits of lifestyle change and weight loss [298].

- [Grade A general population, CF unknown] Adults who are overweight or obese can be advised that modest weight loss reduces cardiovascular risk factors
- [Grade B general population, CF unknown] Adults with sleep apnoea can be advised that improvements in this condition are associated with a 5% weight loss
- [Grade C general population, CF unknown] Adults with musculoskeletal problems, GOR or urinary incontinence can be advised that weight loss of 5% or more may improve symptoms

Assist people to lose weight through lifestyle modification [298].

- [Grade A general population, CF unknown] Adults who are overweight or obese can be strongly recommended lifestyle change – including reduced energy intake, increased physical activity and measures to support behavioural change
- [Grade B general population, CF unknown] Utilise the expertise of the interdisciplinary team for overweight adults and children, and multicomponent approaches as these work better than single interventions (e.g. allied health)
- [Ungraded general population – consensus, CF unknown] Assist adults children and adolescents to get help for disordered eating, poor body image, depression and anxiety and weight-related bullying where these are present
- [Grade C general population, CF unknown] For children and adolescents, focus lifestyle programs on parents, carers and families
- [Grade B general population, CF unknown] For children and adolescents who are overweight or obese, recommend lifestyle change – including reduced energy intake (e.g. encourage drinking of water) and sedentary behaviour (e.g. reduce screen time), increased physical activity and measures to support behavioural change
- [Grade D general population, CF unknown] For children who are managing overweight or obesity, advise that weight maintenance is an acceptable approach in most situations

Additional intensive interventions such as bariatric surgeries should only be considered on an individual basis in people with CF, as the risks may out way the possible benefits and nutritional status greatly compromised.

Monitoring & Evaluation

Regular monitoring of people with CF who have a high BMI is essential. Ideally anthropometric monitoring should take place every three months at routine CF clinic appointments (or more frequently if able). Reviews should include monitoring of eating behaviours, sedentary times, physical activity habits and psychosocial factors. Practitioners may also choose to monitor for additional co-morbidities that may be related high BMI in individuals older than 30 years.

Translating into Practice

- Transition to adult care can sometimes enable a change of focus from the high fat high energy diet to a more nutrient dense, moderate energy diet, particularly if the individual has a BMI >27 kg/m^2 or BMI percentile in the overweight or obese range.
- Assessment of nutritional status, anthropometry and dietary intake should occur as for those who are overweight or obese as those who are at nutritional risk or undernourished.

CHAPTER 7 MACRONUTRIENTS

K. Ford, R. Cavanagh & C. Miles

7.1 Energy, Protein, Fat and Fibre

Historically, CF nutrition guidelines have routinely recommended a high energy and high fat diet [1] due to a high prevalence of undernutrition. Early diagnosis through newborn screening, significant improvements in the nutritional status of CF populations and the emergence of overweight and obesity in some individuals dictate that this approach as a routinely recommended diet needs to be moderated.

This chapter explores the variable energy requirements of people with CF, and the specific role of macronutrients (i.e. carbohydrates, fat, protein and fibre).

Disease Aetiology

An overall deficit in both dietary energy and protein can result in catabolism and undernutrition [301].

ENERGY

A positive energy balance is associated with storage of energy, deposition of tissue, weight gain and normal growth. In contrast, negative energy balance is correlated with depletion of tissue, weight loss and if prolonged, poor linear height, particularly in children [43,301]. In CF, energy balance is complicated by pancreatic insufficiency resulting in malabsorption of fat and protein, which is largely, but not totally, resolved with adequate pancreatic enzyme replacement therapy (PERT).

Most studies looking at energy expenditure in CF refer to resting energy expenditure (REE) due to the significant variability and challenges in measuring in total energy expenditure (TEE). While early studies hypothesise that altered REE in CF is due to a genetically linked abnormality, recent studies have found that altered REE is likely due to disease progression [302]. The following have been reported in the literature in regards to REE in CF:

- Comparison between CF and general population
  - Some studies have found REE is similar in both the CF and non-CF population [33,37,39,303].
  - Most studies report that people with CF have a higher REE compared with controls and predictive values derived from standard equations [30,38,268,304-308].
- Correlation between REE and fat free mass (FFM), pancreatic function and pulmonary function
  - Most studies have found that FFM, pancreatic function and pulmonary function are associated with REE in CF [30,39,41,42,49,309].
  - Some studies found no association between increased REE and lung disease severity [38,305,306,310].
- REE and respiratory exacerbations
  - Some studies have found REE to be increased at the beginning of a CF respiratory exacerbation [32,34,40] while other studies report no change [311,312].
- REE and puberty
  - In comparison to the general population, REE is elevated in both males and females with CF and pancreatic insufficiency during pubertal maturation [38]. This increase in REE has been shown to be greater in females than males [38].
  - REE remains elevated post-puberty in females with CF in comparison to the general population where REE decreases [31,42].

When applying these findings to clinical practice, it is important to remember that an increase in REE may not result in an increase in TEE as the increase in REE may be offset by a reduction in activity in CF, particularly for those with worsening and end-stage lung disease [276].

PROTEIN

Protein is composed of both amino acids and nitrogen and is vital for the structure and metabolic operation of the human body including enzymatic, hormonal and transport functions [43]. Some amino acids cannot be synthesized by the body, and this are referred to as essential amino acids. These essential amino acids must be provided by dietary sources. Importantly, people with CF are known to have decreased protein synthesis (Chapter 6).

FAT

One of the main roles of fat in a CF diet is to provide a concentrated form of energy. Fats also assist in the transportation of fat soluble vitamins and in the formation of phospholipids and adipose tissue [43]. Since the implementation of a high energy and high fat CF diet, the overall caloric intake and growth of people with CF has improved [313,314].

The following should be considered when looking at fat digestion and absorption in people with CF:

- Potential impact of mucous obstructing the pancreas and gall bladder
  - Pancreatic lipase, bile salt and colipase are provided by bile and pancreatic juices and play a key role in the absorption of fat [315].

- Absorption of medium chain triglycerides (MCT)
  - Unlike long chain triglycerides (LCT), which are absorbed via the lymphatic system, MCT are absorbed via the small intestine and transported directly to the liver via the portal vein for metabolism [316].
  - MCTs may be beneficial for people with CF who have cholestasis or short bowel syndrome [317]

FIBRE

Dietary fibre is the edible portion of plant-based foods that is not absorbed in the small intestine but instead undergoes fermentation in the large intestine [43]. Fibre is known to play a key role in optimising digestive and bowel health, reducing cholesterol, and in stabilising blood glucose in the general population [43]. Conversely, little is known about the role of fibre in the CF population. To date, most studies looking at the role of dietary fibre in CF have found conflicting results in regards to adequacy of fibre intake on gastrointestinal symptoms and the incidence of constipation and distal intestinal obstruction syndrome (DIOS) [142,143,318] (Chapter 11).

Assessment

DIET

As part of a thorough nutritional assessment, an individual's intake of energy, protein and fat should be considered. This should be done in conjunction with individual enzyme requirements, anthropometric measures and physical activity levels.

ENERGY

- Refer to Chapter 5 for information on the assessment and calculation of energy requirements for people with CF.
- Macronutrient distribution i.e. percent energy provided by protein, fat and carbohydrate should be considered (see practice points below).

PROTEIN

- Pay particular attention to protein intake in people who are vegan or vegetarian, restrictive eaters and athletes.
- Animal protein sources such as meat, fish, poultry (including eggs) and dairy foods, together with plant sources such as legumes/lentils and nuts are the major dietary protein sources.

FAT

- Oils, margarine, butter, cream, dairy foods, fish, meat, processed foods and takeaway foods are major dietary fat sources.
- Consider the source and quality of the fat ingested i.e. polyunsaturated and monounsaturated versus saturated fats [319].

FIBRE

- Sources of soluble fibre include fruits, vegetables, oats, barley and legumes [320] . Soluble fibre plays a role in lowering of LDL cholesterol [321].
- Sources of insoluble fibre include wholegrain breads and cereals, nuts, seeds, skin of fruit and vegetables . Insoluble fibre adds bulk to stools and also plays a role in the prevention of constipation [321].
- Sources of resistant starch include cooked and cooled potato and rice [320]. Resistant starch ferments in the large bowel and produces short chain fatty acids that play a role in improving bowel health [321].

ALCOHOL

- While not a macronutrient, alcohol intake contributes to total daily energy intake and should be considered as part of a nutrition assessment for adults with CF.

Intervention

Are energy requirements increased in the CF population compared to the general population? PICO 7.1.1

[Grade D] Limited evidence to guide determination of energy requirements for people with CF of all ages. Until further evidence is available, health professionals should be guided by the consensus recommendation of 110-200% of the general population energy target. Use clinical reasoning and an individualised approach to setting energy targets. [30-42]

ENERGY TARGETS

When setting energy targets the aim is to achieve normal nutritional status and growth, whilst avoiding undernutrition or overweight/obesity [1]. It is recommended that practitioners in Australia and NZ consider most recent international recommendation of 110-200% [78] when setting energy targets for people with CF. However, in the absence of strong evidence, this should only be considered a guide.

The following should be considered when assessing and revising individualised energy targets for people with CF [1]:

- Nutritional status
- Dietary intake
- Growth pattern
- Clinical status (including pulmonary function)
- Pancreatic function
- Physical activity levels
- Any additional requirements for weight gain/growth and nutritional repletion
- Increased dietary requirements with pregnancy and lactation
- Likelihood of changes in REE and/or TEE post lung transplant

Are protein requirements increased in the CF population compared to the general population? PICO 7.1.2

[Ungraded] Insufficient evidence to make a recommendation about protein requirements

PROTEIN TARGETS

In the absence of new research, practitioners should use 15-20% of total energy from protein as a guide [78,322]. This aligns with the current recommendations for the general population [43]. A varied diet which meets individual energy requirements should provide adequate protein for people with CF [322].

Additional protein considerations:

- Protein quality
  - Emerging evidence suggests that there should be a strong focus on high-quality protein intake in CF. It has also been proposed that essential amino acid mixtures may be effective in inducing protein anabolism in people in a catabolic state [323,324].

- Intact versus hydrolysed protein
  - There is inadequate evidence to support the use of hydrolysed protein over intact protein for enteral tube feeding in most people with CF [325,326]. For those people with CF and significant CF co-morbidities i.e. GI complications, a more specialised enteral feed that may include partially or fully hydrolysed protein may be appropriate.

- Impact of high protein diet
  - Short-term protein synthesis and thus net nitrogen retention may be increased by a high protein diet (5g/kg/d) [327]. However, this has only been demonstrated in a cohort of stunted paediatric patients and the longer-term implications of a high protein diet are unknown [327].

  - A case report shows an adolescent with CF-related liver disease and portal hypertension developing acute hepatic encephalopathy after consuming 4.5g/kg protein over 6-hours at a festival [328]. Although there is some evidence indicating the need for high-quality protein, further research is needed to assess the optimal level of protein (including essential amino acids) in clinically stable CF children and adults as well as those recovering from acute exacerbations.

What is the evidence to support the routine recommendation of a high fat diet for people with CF? PICO 7.1.3

[Grade D] There were no new studies included in this systematic literature review (2002-2016) to make changes to the existing recommendation for fat intake in CF from the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*'[1]. Continue to recommend an unrestricted diet that contains adequate fat to meet energy requirements. Target an intake of 100g/day if over five years of age based on the premise that a diet high in fat is less bulky and energy targets are more achievable than a diet that is low in fat.

FAT TARGETS

Fat provides a significantly higher amount of energy per gram than the other macronutrients [43].

- Fat = 37kJ/g (9kcal/g)
- Protein and carbohydrate = 16.7kJ/g (4kcal/g)
- Alcohol = 29kJ/g (7kcal/g)

What are the recommendations for fibre in people with CF? PICO 7.1.4

[Ungraded] Insufficient evidence to make a recommendation about fibre intakes.

FIBRE TARGETS

A moderate fibre intake in line with recommendations for the general population may be suitable for people with CF. See Table 7a for further information.

Table 7a. Nutrient Reference Values for Fibre [43] available at https://www.nrv.gov.au/nutrients/dietary-fibre

Patient groups	Adequate Intake (g/day) for fibre	
	Males	Females
Young children		
1-3 years	14	14
4-8 years	18	18
Older children & adolescents		
9-13 years	24	20
14-18 years	28	22
Adults	30	25
Pregnancy		
Adolescents	N/A	25
Adults		28
Lactation		
Adolescents	N/A	27
Adults		30

An alternative and potentially more achievable recommendation for fibre intake in the paediatric population is: Fibre intake (g/d) = age (years) + 5 [329].

ALCOHOL

For adults with CF without a contraindicating condition or medication, advice regarding alcohol should follow the Australian Dietary Guidelines[254] (i.e. no more than two standard drinks on any one day, and no more than four standard drinks on a single occasion). Recommendations for the New Zealand population are available at http://www.health.govt.nz/your-health/healthy-living/addictions/alcohol-and-drugs/alcohol. For some adults with CF, avoidance of alcohol is advised. This may include those with liver disease, pancreatitis, any concurrent condition in which alcohol use is discouraged or contraindicated, and those taking medication where alcohol interacts or is contraindicated. People with CF-related diabetes need to be aware of the risks of hypoglycaemia with alcohol use.

SPORTS NUTRITION CONSIDERATIONS FOR THE CF POPULATION

Advice regarding dietary intake and macronutrient distribution is particularly important for the CF population who are athletes, highly active, engaging in regular exercise and/or working out to improve lean body mass and muscle bulk. It is important that an individualised approach with thorough clinical reasoning is taken when providing sports nutrition advice to people with CF. Specific considerations for the general population that can be applied to CF include;

- Protein requirements of 1.2-2.0g/kg/d are recommended for athletes, with the upper limit of this range recommended for those involved in strength training [330]. Many people with CF are likely to achieve this protein target given the high energy intake of their diet. Consumption of protein above 2g/kg/d is thought to be of no benefit to athletes [330].
- Prior to exercise, encourage food choices that are relatively low in fat and fibre to promote gastric emptying, high in carbohydrate for blood glucose maintenance and are moderate in protein [331]. Where possible, familiar foods that the individual knows is well tolerated should also be encouraged [331].
- For exercise that is greater than one hour in duration, rehydration with a carbohydrate containing beverage is recommended for the non-CF population [331]. However, carbohydrate containing beverages, in particular sodium containing rehydration solutions, may be beneficial for the CF population in exercise of any duration. See Chapter 9 for further information.

- After exercise, advice is tailored around the replacement of losses. A high energy meal or snack with adequate carbohydrate to replace muscle glycogen stores as well as protein to provide amino acids for muscle repair and growth should be encouraged [331]. A carbohydrate to protein ratio of 3-4:1 is recommended by the International Society of Sports Nutrition (ISSN) and 20-25g of high quality protein is recommended by the International Olympic Committee (IOC)[330]. Again, these are reasonable targets for the CF population. Fluid and electrolyte losses should also be replaced after exercise [331]. When providing advice for people with CF who is undertake high intensity exercise and/or body building, it is important the dietitian is aware of the role and use of sports supplements that are available and marketed to these individuals. Sports practitioners and trainers providing nutrition advice to people with CF should be aware of the implications of CF and inform the CF team of any advice they provide.

Monitoring & Evaluation

Macronutrient requirements of people with CF may change over time. This may be due to infective exacerbations, changes in physical activity levels, changes to drug therapies and/or transplantation. It is important that the adequacy of energy, protein and fat intake is reviewed by a dietitian on a regular basis to ensure individual needs are being met[2].

Practice Points PICO 7.1.1

Energy requirements are likely to be elevated for people with CF. Aim for 110-200% of the recommended daily energy intake for age and gender when setting energy targets for the CF population. Take into account the following when setting individualised energy targets for people with CF:

- Nutritional status
- Dietary intake
- Growth pattern – aiming to achieve normal growth (avoid both undernutrition and overweight/obesity)
- Clinical status (including pulmonary function)
- Pancreatic function
- Physical activity
- Any additional requirements for weight gain/growth and nutritional repletion
- Pregnancy and lactation
- Transplantation

Practice Points PICO 7.1.2

Aim for 15-20% energy from protein. Take into account the following when setting individualised protein targets for people with CF:

- Protein intake generally increases as energy intake increases
- A mixed high energy diet should provide adequate protein for people with CF
- Vegans, vegetarians, fussy/restrictive eaters, people with allergies i.e. cow's milk protein allergy and the obese CF population on an energy restricted diet, will require specific dietary advice regarding protein intake

Further research is needed into the impact of protein quality on health outcomes in CF. Protein requirements may be elevated with malabsorption and catabolism. It is particularly important to consider the adequacy of protein intake for people with CF who have signs/symptoms of malabsorption, are unwell e.g. with a respiratory exacerbation or poorly controlled diabetes.

Upper Limit for protein: The NHMRC recommends an upper limit for protein of 25% of energy intake for the general population,[43] however there is no evidence to guide a CF-specific upper limit. Evaluate individual dietary practices contributing to protein intake when intake is above 25% of energy intake; to identify if the high protein intake is contributing to a specific nutritional goal, or if other sources of energy and nutrients can be substituted without compromise to overall nutritional intake and status.

Practice Points PICO 7.1.3

Providing the person is not overweight or at risk of overweight/obesity, avoid restricting fat intake in people with CF

- Aim for 100g/day of fat for people with CF aged >5 years

Take into account the following in setting individualised fat targets for people with CF:

- Source and quality of fat i.e. polyunsaturated and monounsaturated versus saturated fat
  - Potential implications of a high saturated fat diet on cardiovascular health
  - Potential benefits of long chain polyunsaturated fatty acids on inflammation
- Macronutrient distribution
  - Initially aim for 20-30% energy from fat, according to the recommendations for the general population

Up to 35-40% energy from fat is considered acceptable for the paediatric CF population and for those requiring a high energy density diet (e.g. for nutritional repletion).

Practice Points PICO 7.1.4

Aim for a moderate fibre intake in line with the general population recommendations of 14-30g dietary fibre per day. Refer to the Nutrient Reference Values for Australia and New Zealand webpage, https://www.nrv.gov.au/nutrients/dietary-fibre for specific age and gender recommendations.

7.2 Essential Fatty Acids

Research since 2002 has focused on the lipid profile and supplementation of essential fatty acids (EFA). Omega-6 (pro-inflammatory) and omega-3 (anti-inflammatory) polyunsaturated fatty acids are both considered essential as they cannot be synthesised by the human body [43]. EFA disturbances and deficiency are among the many metabolic abnormalities that may affect a person with CF [332-336].

- **Omega-6**
  - mostly comes in the form of linoleic acid (LA), a precursor of arachidonic acid (AA)
- **Omega-3**
  - includes alpha linolenic acid (ALA), a precursor of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic (DPA)

Disease Aetiology

EFA deficiency was first described in CF more than 50 years ago [337]. In CF, fatty acid disturbances are largely characterised by lower LA and DHA concentrations in the serum, plasma, erythrocytes or whole blood [336-338]. The metabolism of AA is also thought to be altered in some people with CF [335,339].

Hypotheses looking at the aetiology of EFA deficiency in CF have changed over time. It was initially thought that EFA deficiency in CF was a consequence of malnutrition, pancreatic insufficiency and fat malabsorption [335]. More recent studies report that altered fatty acid composition in CF is likely due to intrinsic metabolic alterations that occur in cells lacking cystic fibrosis transmembrane conductance regulator (CFTR) function [338]. The precise mechanism and significance of EFA deficiency in CF remains unclear [338]. The overall prevalence of EFA deficiencies in CF remains unknown.

EFA disturbances may have significant consequences on the progression of CF. Animal studies have shown that EFA deficiencies can impair lung defence mechanisms [335,340,341]. The postulated links between EFA deficiency and inflammation in CF are:

- Inflammation related to increased production of pro-inflammatory AA derived eicosanoids [335]
- The reduction in anti-inflammatory benefits associated with reduced DHA levels [335]

The impact of EFA disturbances on CF health outcomes were also recently summarised in the 2016 ESPEN guidelines [78] whereby the following was noted:

- LA deficiency is correlated with poor growth and pulmonary status in the paediatric population
- Elevated AA to DHA ratio is associated with impaired bone mineral density
- EFA deficiencies are found to be positively correlated with impaired immune, hepatic and renal function

Assessment

DIET

Review dietary sources of EFAs

PLANT-BASED SOURCES

- Provide ALA (omega-3)
- Found in plant-based fats and oils such as canola oil and soybean oil, and also in linseeds, chia seeds and walnuts [43]

ANIMAL (MARINE) BASED SOURCES

- Provide EPA and DHA
- Predominantly found in oily fish such as salmon, sardines, blue-eye trevalla, mackerel, herring, canned salmon, canned sardines and some varieties of canned tuna [43]

CLINICAL

EFA SUPPLEMENTATION

- Check for any use of EFA supplementation including fish oils

EFA DEFICIENCY

Signs and symptoms of inadequate EFA intake may include [342-347]:

- Rough and/or scaly skin
- Dermatitis
- Increased trans epidermal water loss
- Increased susceptibility to infection
- Impaired wound healing
- Thrombocytopenia and reduced platelet aggregation
- Poor growth
- Learning difficulties (in children)

BIOCHEMICAL AND LABORATORY DATA

SERUM EFA PROFILE

Measurement of serum levels of EFA is generally only undertaken in a research setting with the following most often reported [43,78]:

- Serum LA
- Triene : tetraene (T3:T4)

Intervention

LIPID PROFILES

Preliminary research shows that dietary fat intake patterns of children with CF may directly influence lipid profiles, suggesting that changes in dietary practices, particularly promotion of omega-3 containing foods, may result in better fatty acid profiles resulting in improved clinical outcomes and inflammation [334,348]. Conversely, another study concluded that adjusting intake of dietary fat patterns is unlikely to affect lipid profiles [349]. More research is needed in this area before any practice recommendations can be made.

Does dietary supplementation with omega-3 essential fatty acids improve health outcomes in people with CF? PICO 7.2.1

[Grade C] Dietary supplementation with omega-3 fatty acids may improve health outcomes for people with CF, however, the evidence is insufficient to recommend routine use of omega-3 supplementation. [44-46]

EFA SUPPLEMENTATION

The body of evidence regarding omega-3 supplementation in CF lacks consistency due to significant variability in dosing, biochemical analysis of EFA and outcome measures. Long term safety and efficacy data as well as PERT recommendations with omega-3 supplementation in CF is also lacking [350]. As a result, until larger clinical trials have been completed, routine supplementation of omega-3 fatty acids is not recommended for the CF population [350].

Despite a lack of evidence to support additional omega-3 supplementation in CF, it is still important that people with CF meet fatty acid recommendations for the general population. The National Heart Foundation recommends the following [351]:

- Aim to eat 2-3 serves of fish (including oily fish) per week
- Aim to eat 1000mg of plant-based omega-3 per day
- Consume a healthy diet that includes vegetables and legumes, fruit, wholegrain cereals, lean meats and their alternatives, nuts and seeds, milk, cheese and yoghurt and healthier fats and oils.

EFA SAFETY CONSIDERATIONS

Omega-3 EFA supplementation must be commenced with some caution, as intakes above 5000mg per day have been associated with the following [336,352]:

- Oxidative stress, leading to an increased requirement for dietary antioxidants
- A sensation of fullness
- Cramping, abdominal pain, steatorrhea and nausea

In CF there have also been some reports of steatorrhea and abdominal pain with omega-3 EFA supplementation, however, there have also been many studies which report no adverse events with supplementation [353-355]. Overall there is an absence of data on the long-term efficacy of omega-3 EFA supplementation in the CF population.

Monitoring and Evaluation

The adequacy of EFA intake, particularly omega-3 EFAs should be considered as part of the annual nutrition assessment. More regular review is suggested for people with CF who show signs and symptoms of EFA deficiency.

Practice Points PICO 7.2.1

People with CF may be at risk of EFA deficiency

- The prevalence of EFA deficiency in CF is unknown

Omega-6 fatty acids - Includes linoleic acid (LA), a precursor of arachidonic acid (AA)

- LA occurs in seed oils (sunflower, safflower and corn)
- AA occurs in meat, poultry and eggs
- Can exert a pro-inflammatory effect

Omega-3 fatty acids – Includes alpha linolenic acid (ALA), a precursor of the long-chain PUFAs (Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA))

- ALA occurs in legumes, canola oils, margarine, linseed oils and nuts (walnuts)
- Long-chain omega-3 PUFAs occur in fish oils
- Known for their anti-inflammatory properties

Source of supplementation

- Insufficient evidence to suggest that any type or combination of omega-3 EFA (dietary or commercial) is superior.

Take into account the following prior to recommending omega-3 supplements to people with CF:

- Safety – intakes above 5000mg/d have been associated with an increase in oxidative stress and gastrointestinal discomfort
- Efficacy – long term efficacy of omega-3 supplementation in CF is unknown
- Cost of commercial omega-3 supplements
- Impact on burden of treatment and adherence

May be better tolerated with meals (and PERT)

CHAPTER 8 FAT SOLUBLE VITAMINS

J. Anderson & T. Katz* (* Authors contributed equally to this chapter)*

Maintaining optimal fat soluble vitamin status is important for people with CF [356,357]. Fat soluble vitamins include:

Vitamin A – vital for night vision and good immune function [358]
Vitamin D – fundamental to good bone health [359]
Vitamin E – an important antioxidant [357]
Vitamin K – vital for normal blood coagulation and important for good bone health [360]

People with CF, particularly the pancreatic insufficient population, are at risk of fat soluble vitamin deficiencies. Of particular concern, is that fat soluble vitamin deficiencies, both subclinical and overt, may be associated with generalised poorer clinical status [1]. Common factors contributing to fat soluble vitamin deficiencies in CF are outlined in Figure 8a [1].

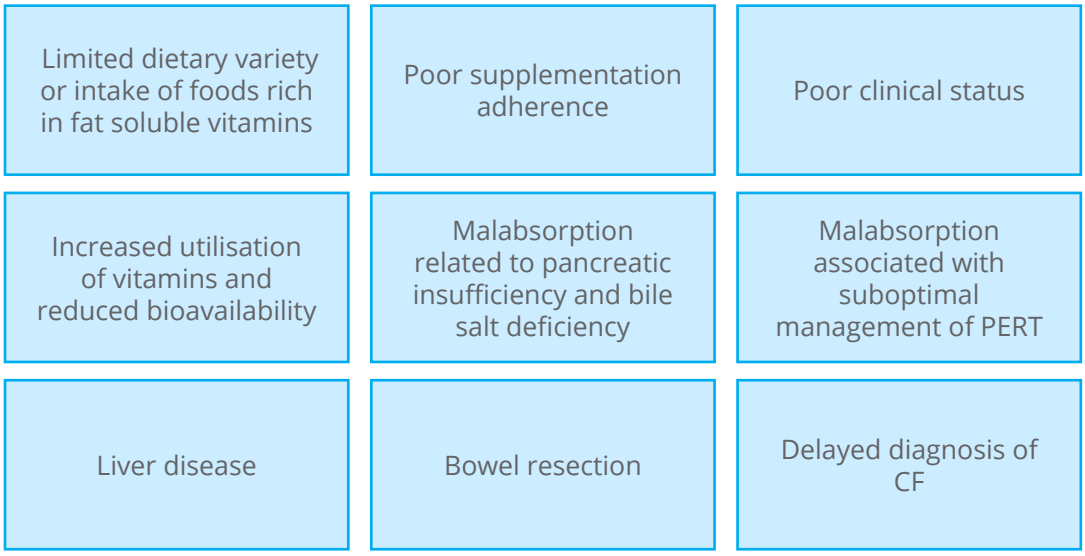

Figure 8a. Potential factors contributing to fat soluble vitamin deficiency in CF

This chapter should be read in conjunction with Chapter 11 and Chapter 14 for fat soluble vitamin assessment, supplementation and monitoring in CF-related liver disease and pregnancy respectively.

In Australia and NZ, unlike other countries, there is currently only one CF-specific multivitamin available for routine supplementation that contains all four fat soluble vitamins (A, E, D and K) - namely VitABDECK®. It is important to note that VitABDECK® is water-miscible and also contains vitamins B, C and zinc. The composition of VitABDECK® and other fat soluble multivitamin preparations available are outlined in table 8a below. Practitioners may also choose to use single fat soluble vitamin preparations as shown in table 8b. The smallest number of preparations as possible should be recommended to limit patient medication burden.

Table 8a. Composition of fat soluble multivitamin preparations available in Australia & NZ**

Product	Type	Dose	Vitamin A (IU)	Vitamin D (IU)	Vitamin E (IU)	Vitamin K (µg)
VitABDECK®*	Capsule	per capsule	2 500	440	150	150
Bio-Logical A & E Solution®**	Liquid	per ml	2200	-	102	-
Bio-Logical A, D & E Solution®(Aus only)	Liquid	per ml	2188	1000	102	-
Vitamin A with C & D**	Liquid	per ml	6660	1440		

Units provided according to international terminology [361] **VitABDECK also contains 3mg β-carotene (1665IU) **NZ full prescription subsidy http://www.pharmac.govt.nz/Schedule*

Table 8b. Composition of fat soluble single vitamin preparations available in Australia & NZ*

Product	Type	Dose	Vitamin A (IU)	Vitamin D (IU)	Vitamin E (IU)	Vitamin K (µg)
Vitamin A	Liquid	per ml	2200	-	-	-
	Drops	per drop	2500	-	-	-
	Capsule	per capsule	5000	-	-	-
	Tablet	tablet	50 000	-	-	-
Vitamin D	Liquid	per ml	-	1000	-	-
	Drops	per drop	-	1000	-	-
	Capsule	per capsule	-	1000		-
	Tablet	per tablet	-	50 000	-	-
	Capsule*	per capsule		50 000		
Vitamin E	Liquid	per ml	-	-	102	
	Capsule	variable	-	-	100, 200, 250, 500	-
	Liquid*	per ml			156	
Vitamin K	Capsule	variable	-	-	-	100, 10 000
	Liquid, Injection or oral use*	per 0.2ml ampule				2000

Units provided according to international terminology [361] **NZ full prescription subsidy http://www.pharmac.govt.nz/Schedule*

8.1 Vitamin A

J. Anderson & J. Graves

Vitamin A contains a number of fat soluble compounds, has antioxidant properties [43,362], and plays an integral role in vision, immunity, epithelial cell integrity, pulmonary function, growth, bone health and reproduction [57,363] .
There are two main forms of vitamin A:

- Preformed vitamin A (retinol, retinal, retinoic acid and retinyl esters) is the most active form of vitamin A. It is mostly found in animal food products such as liver, kidney, egg yolk and in the fat of dairy products. It is also found in fortified margarines and breakfast cereals [1,43,363].
- Provitamin A carotenoids (β-carotene, α-carotene and β-cryptoxanthin) are dietary precursors of retinol [43,362]. β-carotene is the most common of the carotenoids and is found in green leafy vegetables, in red, orange and yellow fruits and vegetables and in oils [43,363].

Disease Aetiology

VITAMIN A DEFICIENCY

In addition to the factors outlined in figure 8a, additional risk factors for vitamin A deficiency in CF include increased oxidative stress due to chronic inflammation and frequent infections [362,364].

Up to 60% of infants with CF have suboptimal vitamin A status at time of diagnosis [47,71,365]. Subclinical vitamin A deficiencies may also affect up to 45% of children and adults with CF [51,53,60]. Low β-carotene levels are particularly common during pulmonary exacerbations [48,366-370]. While the significance of subclinical deficiency is not clear, there is some evidence that low vitamin A status may have negative effects on pulmonary function and oxidative status [52,58,60,366,370]. Documented cases of overt clinical vitamin A deficiency in people with CF are rare. However, occasional reports of night blindness and xeropthalmia occur [371-373].

VITAMIN A TOXICITY

Vitamin A toxicity is rare, however, is of increasing concern to the CF population due to use of water-miscible vitamin A supplements with higher doses of preformed vitamin A [56-58,374].
Factors known to increase the risk of vitamin A toxicity in the general population include [43,363]:

- Underlying liver disease
- Underlying kidney disease
- Hyperlipidemia
- Alcoholism
- The use of some drugs i.e. tetracyclines; acne drugs such as Isotretinoin e.g. Roaccutane®

There is some evidence in the non-CF population that high dose β-carotene supplementation may be harmful for smokers [43]. However β-carotene is generally considered of low toxicity with no documented levels of excessive intake in people with CF [43,362,364].

See Chapter 14 for supplementation of vitamin A during pregnancy

Assessment

DIET

When assessing dietary intake of vitamin A, it is important to consider the following:

- Intake of foods rich in vitamin A. See tables 8c and 8d below for examples
  - Particular attention to preformed vitamin A
- Cooking methods
  - The bioavailability of carotenoids is improved with cutting foods into smaller pieces, using moderate cooking temperatures and using oil in the preparation of foods [43,362]
- Intake of ONS and enteral nutrition support
- Use of over-the-counter complementary therapies which are often high in vitamin A (e.g. cod liver oil)
- Currently prescribed fat soluble vitamin preparations
- Formulation (fat vs. water-miscible)
- Composition (percentage preformed vitamin A)
- Preformed water-miscible formulations are more bioavailable and pose a greater risk of vitamin A excess [359,375].

Table 8c. Preformed vitamin A (retinol) containing foods* [376]

	Serving size	Retinol content (mg) per serve	Retinol content (mg) per 100g
Lamb liver, raw	100g	33.33	33.33
Chicken liver pate	100g	9.94	9.94
Polyunsaturated margarine	1 tspn	0.05	1.02
Butter	1 tspn	0.04	0.90
Double cream	1 tspn	0.04	0.72
Raw egg yolk	1 yolk	0.78	0.49
Sour cream	1 tbspn	0.20	0.42
Cheddar cheese	20g	0.62	0.31
Full cream milk	1 cup	0.13	0.05

* Refer to the Translating into Practice box at the end of this section for information on conversion between mg and IU.

Table 8d. Provitamin A (β-carotene) containing foods [376]

	Serving size	β-Carotene content (mg) per serve	β-Carotene content (mg) per 100g
Sweet potato	1 medium 420g	27.70	6.60
Sweet potato, orange flesh boiled	1/2 cup	6.30	6.00
Carrot, raw	1 medium 130g	7.79	5.99
Kumara (NZ), cooked	1/2 cup cooked	3.83	3.53
Parsley, raw	2g pinch	0.06	3.81
Tomato paste	1 tspn	0.16	2.90
Dried apricot	2 apricots	0.16	2.37
Watercress, raw	1 cup	0.65	1.98
English spinach, raw	1 cup	0.88	1.96
Mango	1 medium - 294g	4.20	1.43
Red chili, raw	1 small	0.07	1.37
Chinese cabbage	1 cup	1.43	1.36
Cos lettuce	1 cup	0.60	1.21
Pumpkin, butternut, raw	1 cup	1.45	1.21
Rockmelon	1 cup	1.41	0.83
Tomato, raw	1/2 cup	0.52	0.50
Peach, raw	1 x 140g	0.61	0.40
Nectarine, raw	1	0.50	0.40
Watermelon	1 cup	0.67	0.42
Prune	2 prunes	0.64	0.40
Passionfruit	1 fruit	0.65	0.36
Orange	1 x 150g	0.12	0.08

***** Refer to the Translating into Practice box at the end of this section for information on conversion between mg and IU.

CLINICAL

Signs and symptoms of vitamin A deficiency include:

- Abnormal dark adaption (night blindness) [359,365]
- Xerophthalmia (dryness, fragility and clouding of the cornea) [359,365]
- Poor bone growth [365]
- Non-specific dermatological problems [365]
- Impairment of the immune system [365]
- Anaemia and anorexia [363,365]

Signs and symptoms of vitamin A toxicity are rare, diverse and may include [377]:

- Dry skin
- Nausea
- Headache
- Fatigue
- Irritability
- Ataxia

- Alopecia
- Bone and muscle pain
- Reduced bone mineral density
- Visual impairments
- Hepatomegaly and hepatotoxicity

People who consume large amounts of β-carotene may develop yellow tinged skin (carotenemia) without developing vitamin A toxicity [377]. As previously mentioned, when assessing for the risk of vitamin A deficiency or toxicity, consider all potential sources of vitamin A.

BIOCHEMICAL AND LABORATORY DATA

How should vitamin A be assessed for people with CF? PICO 8.1.1

[Ungraded] There is insufficient evidence to make a CF-specific recommendation about assessing vitamin A status.

In the absence of evidence health professionals should continue to use serum retinol when assessing vitamin A status. Explore the addition of tests to assist with the interpretation of vitamin A status including, zinc, retinol binding protein (RBP), an inflammatory marker and retinol : RBP molar ratio, though there is limited evidence for their use in CF. Serum retinyl esters may be tested for the assessment of vitamin A toxicity. There is no evidence to recommend the routine assessment of β-carotene.

There are no non-invasive, readily available tests to assess vitamin A tissue stores [285,365]. As a result, despite serum retinol being an insensitive marker, it remains the most common measure of vitamin A status for both the general and CF populations.

Considerations when using serum retinol to assess vitamin A status:

- Retinol is primarily stored in the liver and is transported to where it is needed in the tissues bound to retinol binding protein (RBP), a protein synthesised in the liver [359].
- Serum retinol and RBP are negative acute phase reactants and are likely to be transiently decreased during a pulmonary exacerbation. For this reason, practitioners should aim to measure vitamin A status during periods of clinical stability [57,60,61,365].
- There are considerable variations between studies and laboratories in the reference ranges and cut-offs used to define vitamin A deficiency. Results should always be interpreted using the reference ranges provided by the laboratory performing the test.
- There is some evidence that higher recommended serum retinol levels may be required to optimise clinical outcomes in CF [52,58].
- Assessment of the molar ratio of retinol : RBP may assist in the interpretation of vitamin A status (see translation into practice below) [371,377-379]
    - Suggested deficiency: ratio <0.8
    - Risk of toxicity: ratio >1.0 (indicates free retinol not bound to RBP) and thus risk of toxicity
- Zinc is required for the hepatic synthesis of RBP. Furthermore, zinc deficiency may lead to decreased RBP in the plasma and low serum retinol levels [365]. Correction of zinc deficiency may improve low serum retinol [372].
- Serum retinol levels increase post-prandially and can reflect recent vitamin A ingestion [380]. Ideally fasting levels should be measured where possible.

Another laboratory test that can assess vitamin A status is serum retinyl esters (fasting). This test is a stronger marker of excess vitamin A than serum retinol but it is not routinely available in the clinical setting [359,377,378,381]. Vitamin A status is considered abnormal if more than 10% of the total vitamin A pool is in the form of serum retinyl esters [378,381].

Intervention

What is the role for routine supplementation of vitamin A in people with CF and pancreatic insufficiency? PICO 8.1.2

[Grade D] Routine supplementation of vitamin A in all people with CF and PI is recommended (table 8e) (unchanged from the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*')[1].

There is inadequate evidence at this time for the routine adjunctive supplementation of β-carotene as an antioxidant. [47-61]

The evidence is unclear regarding the need for routine versus individualised supplementation of vitamin A in people with CF and pancreatic insufficiency. Whilst some evidence suggests that routine supplementation is required, other evidence suggests that not all people with CF and pancreatic insufficiency require supplements and that supplementation should be individualised based on serum levels.

In the Australian and NZ context, current practice to routinely supplement all pancreatic insufficient individuals with vitamin A should continue (as outlined in Table 8e) to:

- aim for the normal range of serum retinol for healthy individuals
- monitor for any new supplements or changes to supplement formulations available [1]

Consider supplementation on an individual basis for the pancreatic sufficient population.

Table 8e. Recommended daily doses of vitamin A supplementation for pancreatic insufficient people with CF [1].

Age	Recommended Vitamin A supplementation (IU)
Infants	1500 – 2000
Young children	1500 – 5000
Older children, adolescents and adults	2500 – 5000

Refer to the Nutrient Reference Values for Australia & New Zealand for the vitamin A recommended dietary intake values for the general population [43].

What vitamin A supplementation dose should be prescribed to treat vitamin A deficiency in people with CF? PICO 8.1.3

[Grade D] In the absence of quality evidence for supplementation to treat subclinical vitamin A deficiency in people with CF, it is recommended to follow the doses recommended in the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*'[1] as outlined in Table 8e.

There is no evidence specific to people with CF for supplementation to treat severe deficiency. Assess supplementation on an individual basis with interdisciplinary input and referral to relevant disciplines outside of CF as appropriate.

SUBCLINICAL DEFICIENCIES – USE THE DOSING RECOMMENDATIONS OUTLINED IN TABLE 8E.

Vitamin A deficiency, refractory to treatment with recommended levels of vitamin A supplementation, may benefit from an empiric trial of zinc [78,372]. See Chapter 9 for zinc supplementation recommendations for the general population in Australia and NZ [43].

SEVERE VITAMIN A DEFICIENCY (AS REFLECTED BY THE PRESENCE OF CLINICAL SYMPTOMS SUCH AS NIGHT BLINDNESS)

High dose vitamin A supplementation will likely be required [371,372]. An individualised treatment and monitoring plan is required when considering high dose supplementation, with interdisciplinary input from a CF physician, dietitian and relevant practitioners outside of CF, including a gastroenterologist ideally with CF experience.

What is the safe upper limit for vitamin A supplementation in people with CF? PICO 8.1.4

[Ungraded] There is insufficient evidence available regarding the safe upper limit for vitamin A supplementation in CF. In the absence of evidence specific to CF, health professionals should be guided by recommendations for the general population.

Current recommendations for the upper level of intake for vitamin A as retinol for the general Australian and NZ population can be seen in table 8f below [43]. There is insufficient evidence to establish an upper limit for β-carotene for supplemental use [43]. Regular monitoring of retinyl esters can assist in identifying vitamin A toxicity with high dose supplementation [60,377,381].

Table 8f. Recommended upper limit of vitamin A intake as retinol.

Age	Upper limit for vitamin A (IU)
Infants	2000
Young children	2000 - 3000
Older children	5667
Adolescents	9333
Adults	10 000
Pregnancy	9333 - 10 000

High dose supplementation doses used to treat severe vitamin A deficiency may exceed general recommended upper limits. In such circumstances, caution needs to be used, secondary to the risk of toxicity and inability to accurately measure liver reserves. Vitamin A supplementation in excess of recommended upper limits should only be considered after a thorough interdisciplinary assessment of the potential risks and benefits.

Where potential toxicity is a concern, it is recommended to provide additional supplementation in the form of β-carotene as excessive ingestion of this form is generally considered safe [78,371]. The ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis provide information on additional β-carotene dosing[78]. See Chapter 11 for vitamin A supplementation in CF-related liver disease and Chapter 14 for pregnancy.

Monitoring and Evaluation

How often should vitamin A levels be measured in people with CF? PICO 8.1.5

[Ungraded] There is insufficient evidence available to recommend specific monitoring and evaluation protocols for vitamin A levels in CF. Health professionals should continue to follow recommendations in the '*2006 Australasian Clinical Practice Guidelines for Nutrition in* CF', to assess annually and monitor more frequently in those at high risk of deficiency or toxicity[1].

Monitoring of vitamin A status should be completed during the annual CF review, however more frequent monitoring may be required in those at higher risk of deficiency or toxicity and should be considered on a case-by-case basis [1]. People with CF-related liver disease, history of intestinal resection or malabsorption, on certain medications such as Roaccutane®, recent changes in vitamin supplementation regimen, and/or poor treatment adherence (especially to PERT and prescribed vitamins) are all considered to be at higher risk. Regular review by relevant members of the interdisciplinary team and a gastroenterologist is suggested for people on high dose preformed vitamin A supplementation.

Translating into Practice - Conversions

Different forms of vitamin A need to be converted to consistent units in order to be compared. Units used to express equivalence include International Units (IU) and retinol equivalents (RE). (Retinol activity equivalents (RAE) are used in the USA).

1 retinol equivalent = 1 µg retinol = 6 µg β-carotene[1] = 3.33IU vitamin A

Vitamin A status is usually measured as serum retinol and reported as µmol/L in Australia and NZ. However units of measurement may differ internationally. Converting serum retinol:

mg/L = 3.496µmol/L
µg/dL = 0.035µmol/L

To calculate retinol : RBP molar ratio, ensure both retinol and RBP are in the same units i.e. µmol/L by using the following conversions:

- To calculate Retinol µmol/L: multiply retinol µg/L x 0.0035
- To calculate RBP µmol/L: multiply RBP mg/L x 0.0476 [378]
  Note: serum retinol will most likely already be in the correct units i.e. µmol/L

Interpret the retinol : RBP ratio as follows:

- Likely deficiency = ratio <0.8
- Normal = ratio 0.8-1.0
- Likely toxicity = ratio >1.0 [371]

Practice Points PICO 8.1.1

Serum retinol is the most common and readily available measure of vitamin A deficiency status, however there is significant variability in what is used to define deficiency, adequacy and excess.

- Interpret results using reference ranges provided by the laboratory doing the test.
- Where possible measure levels when clinically stable. Acute illness may result in decreased serum retinol.
- Ideally measure when fasting. Non-fasting levels may reflect recent intake of vitamin A.

If low serum retinol levels despite recommended supplementation consider:

- Adherence with recommended vitamin supplementation
- Whether supplements are being taken with PERT and fat containing meal

Measure the following to assist in the interpretation of serum retinol;

  - A marker of inflammatory status such as CRP
  - Zinc
  - Retinol binding protein (RBP)
  - Other fat soluble vitamin levels
- Acute illness / increased inflammation will result in increased inflammatory markers and decreased levels of serum retinol, zinc and RBP.
- If retinol, zinc and RBP are all low in the setting of raised inflammatory markers, then results most likely reflective of acute illness not vitamin status. Recommend re-assess levels when patient clinically stable.
- If serum retinol is still low despite normal inflammatory markers, serum zinc and RBP, measure the molar ratio of RBP : retinol. This will assist in the interpretation of retinol levels and the adequacy or excess of supplementation. A ratio <0.8 suggests deficiency of vitamin A. Supplement vitamin A as per recommendation 8.1.3 and practice point 8.1.3.
- If serum zinc is low or zinc status assessed as likely deficient, supplementation of zinc may be beneficial. Note that serum zinc is not a sensitive or specific test of zinc status and zinc may be normal even with subclinical zinc deficiency (Chapter 9).
- If RBP is low in the setting of normal inflammatory markers, be cautious with high dose supplementation, particularly in those with CF-related liver disease. Gastroenterologist advice is recommended (Chapter 11).

Enquire about symptoms such as poor night time vision if deficiency is suspected. Poor night vision will manifest prior to xeropthalmia.

If high serum retinol;

- Consider if fasting levels. High levels may reflect recent intake of vitamin A.
- Assess Retinol : RBP ratio. A ratio >1.0 may indicate excess intake and toxicity.

If the person with CF is on high dose supplementation and at risk of vitamin A toxicity;

- Assess Retinol : RBP ratio. A ratio >1.0 may indicate toxicity

Measure serum retinyl esters as a function of total serum retinol. Serum retinyl esters >10% of the total vitamin A pool are usually considered abnormal.

[1] There is ongoing debate regarding conversion factors for carotenoids. Australia and NZ have maintained traditional conversion rates more aligned with sources of carotenoids in our diet, whereas conversion rates are double in the US. Note 1 RAE = 1 µg retinol= 12 µg β-Carotene

Practice Points PICO 8.1.2

For people who are pancreatic insufficient fat soluble vitamin supplementation should be commenced at diagnosis and, if indicated, continued throughout life. Aim to achieve serum retinol levels within the normal population reference ranges.

'2006 Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis'[1]:

- Infants: 1500-2000 IU vitamin A /day
- Young children: 1500-5000IU vitamin A /day
- Older children, adolescents and adults: 2500-5000IU vitamin A / day

Evaluate the need for supplementation on an individual basis for the pancreatic sufficient population.

Practice Points PICO 8.1.3

- In cases of subclinical deficiency supplement as per table 8e (Chapter 8) above guidelines aiming to achieve serum retinol levels within the normal population reference ranges.
- If RBP : retinol ratio indicates deficiency i.e. <0.8, increase supplementation to upper limits of recommended supplementation e.g. adults to 10 000IU.
- Low RBP may occur in those with severe liver disease. Be cautious with high dose supplementation in these circumstances. Recommend consultation by gastroenterologist. See chapter 11 for supplementation recommendations in CF-related liver disease.
- For vitamin A deficiency refractory to upper level of recommended supplementation, think about an empiric trial of zinc supplementation. See chapter 9

Severe vitamin A deficiency with overt symptoms will require high dose supplementation (>10 000IU). An individualised approach with interdisciplinary input including CF physician, dietitian and appropriate other health professionals such as gastroenterologist is recommended.

Practice Points PICO 8.1.4

Be guided by upper limits for the general population. Note upper limits are for preformed vitamin A as retinol. Australian and New Zealand Nutrient Reference Values (2006) [43];

- Infants: 2000 IU vitamin A
- Young children: 2000 – 3000 IU vitamin A
- Older children: 5667 IU vitamin A
- Adolescents: 9333 IU vitamin A
- Adults: 10 000 IU vitamin A

Supplementation for severe vitamin A deficiency may require doses greater than the above recommended upper limits. Supplementation doses in excess of these upper limits should be advised with caution and only following a thorough interdisciplinary assessment of potential risks and benefits. Referral to a gastroenterologist with CF experience is recommended.

- Where vitamin A toxicity is a concern, consider additional supplementation in the form of β-carotene, as excessive ingestion of this form is generally considered safe.
- In the absence of an available β-carotene supplement, a regular multivitamin with greater proportion of vitamin A as β-carotene may be considered. However additional supplementation of other fat soluble vitamins may be required, with an increase cost and burden to person with CF.

Monitor serum retinol, RBP, retinol : RBP ratio and if available serum retinyl esters for those on high dose supplements.

Practice Points PICO 8.1.5

Monitor vitamin A status annually. More frequent monitoring (e.g. 3-6 monthly) is suggested in the following scenarios:

- After changing supplementation doses, especially after high dose supplementation
- For people with CF-related liver disease or history of intestinal resection or malabsorption
- In people with poor adherence to PERT and fat soluble vitamin supplementation
- After changes to treatment for malabsorption where a change in the level of fat absorption has occurred

On some drugs such as acne medications e.g. Roaccutane®

8.2 Vitamin D

T. Katz

There has been an increased focus on vitamin D and people with CF in the scientific literature in the last decade. Of particular focus has been the relative efficacy of cholecalciferol versus ergocalciferol, the ideal level of serum vitamin D and more recently the potential effects of vitamin D beyond bone health. In this section, where the CF literature is lacking, reference has been made to key documents that represent a consensus amongst experts in Australia and New Zealand, specifically the Australian and New Zealand Bone and Mineral Society (ANZBMS) and Osteoporosis Australia.

Vitamin D refers to ergocalciferol, D_2 (derived from plant sources) and cholecalciferol, D_3 (derived from animal sources). Cholecalciferol is also formed through the action of ultraviolet B radiation (UVB) on 7-dehydrocholesterol in the skin [69], this is the most significant contributor to an individual's vitamin D status.

Vitamin D is responsible for calcium absorption from the gut and subsequently for optimal bone health and muscle function [69]. Without adequate vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus are absorbed [382]. Non-classical functions of vitamin D are an emerging area of research and include the potential impact on other comorbidities such as pulmonary function [62,64-68], depression [383], and the development CF-related diabetes [384].

Is vitamin D status associated with measures of respiratory health (lung function, pulmonary exacerbations, markers of inflammation) in people with CF? PICO8.2.1

[Grade D] At this stage there is insufficient evidence that vitamin D status is associated with measures of respiratory health in people with CF. [62-68]

Disease Aetiology

VITAMIN D DEFICIENCY

Vitamin D deficiency is not confined to people with CF and usually relates to situations of decreased sun exposure or decreased synthesis rather than due to poor dietary intake. Deficiency rates amongst adults without CF in Australia have been reported to be as high as 50% [69]. Risk factors in the general population include [382]:

- Fair skin
- Dark skin - unable to synthesize cholecalciferol from UVB as efficiently
- Clothing - people who dress modestly – e.g. for religious reasons
- Exclusively breastfed infants whose mother is vitamin D deficient or is considered at high risk of deficiency
- Profession - people who work indoors
- Geographical location – people who live in the southern most states or South Island of NZ
- Sunscreen with a protection factor of 30 also reduces vitamin D synthesis by 95% [385]

Despite routine supplementation, Vitamin D deficiency in people with CF is common in Australia and NZ, with a reported incidence of 33% in the newborn period [71] and between 17-56% in older children in Australia [51,79]. Additional risk factors for people with CF include:

- Potential poor adherence to prescribed vitamin D supplements
- Potential impaired absorption of fat soluble vitamins (from the diet or supplements) [53,73,75,77]
- Decreased sunlight exposure (intentional avoidance due to drug induced photosensitivity or due to decreased activity and hospital admissions) [73,75,77]
- Potential impaired hydroxylation of cholecalciferol to 25(OH)D in the liver [53,75]
- Low vitamin D binding protein [53,386]
- Potential for impaired conversion of previtamin D_3 into vitamin D_3 secondary to known phospholipid membrane composition abnormalities and/or CFTR dysfunction in the skin [53]
- Use of some medications which increase vitamin D metabolism (e.g. rifampicin and corticosteroids)

Retrospective audits provide some additional information on factors that may be associated with lower vitamin D levels, however it is important to remember that these are not causal. Numerous studies have reported a significant negative correlation with age [64,65,67,72,74-76]. Most of these were paediatric studies showing that adolescents are more likely to be deficient than younger children.

Osteoporosis Australia defines vitamin D deficiency at the following 25(OH)D concentrations [387]:

- Mild deficiency (30-49 nmol/L)
- Moderate deficiency (12.5-29 nmol/L)
- Severe deficiency (<12.5 nmol/L)

VITAMIN D TOXICITY

Toxicity has been described in the general population, however no studies could be found in the CF population. Considerations when assessing for risk of vitamin D toxicity include:

- Toxicity can occur through excess supplementation but not through sun exposure [77]
- Risk of toxicity increases when serum 25(OH) D concentrations exceed 220 nmol/L [69] or 250 nmol/L [77].
- An autosomal recessive mutation in the general population has been identified which affects the conversion of excess cholecalciferol to its inactive form therefore increasing the risk of hypercalcaemia [388]. For this reason some hospitals have advised against the use of high dose treatment such as multiple doses of 50 000 IU (known as STOSS therapy)

Assessment

Sunlight is the major source of vitamin D in Australia and NZ. The amount of sunshine needed depends on skin colour, location and season [387]. Less vitamin D is synthesised in winter, especially at latitudes further from the equator [69].

- Assess exposure to the sun, ask questions about time spent outdoors, consider time spent in hospital or in an office
- Consider clothing (especially those who dress modestly – e.g. for religious reasons)
- Consider location of an individual in terms of latitude and UVB exposure

DIET

Estimated daily intake for adults in Australia is only 80-120 IU a day and is likely to be similar in NZ, much lower than in the US and Canada where foods are permitted or mandated to be supplemented [69]. Food sources of vitamin D are limited and individuals are unlikely to obtain more than 5-10% of their total vitamin D requirement from their diet [69].

Foods with some vitamin D content include fatty fish such as salmon, herring and mackerel, liver and eggs. Margarine is the only food that requires mandatory fortification in Australia and makes a small contribution to the Australian diet. This mandatory requirement does not apply to NZ [43]. Cod liver oil is another source of vitamin D but it should be used with caution as it also contains vitamin A which can be toxic.

It is important to note the method of feeding in infants as breast milk has very little vitamin D while formula is supplemented [43]. Likewise enteral feeds and oral nutritional supplements contain significant amounts of vitamin D. Finally, all forms of supplemental vitamin D including vitamin D only preparations, general multivitamins and CF-specific fat soluble vitamin preparations should be assessed.

CLINICAL

Signs and symptoms of vitamin D deficiency can include:

- Decreased bone mass in children [77,78,149]
- Rickets in young children [382]
- Failure to achieve peak bone mass in adolescents [77]
- Osteopaenia and osteoporosis in mature adults [77,382]

Clinical features of vitamin D toxicity include hypercalciuria and hypercalcaemia [389,390] which can present as:

- Poor appetite
- Weight loss
- Gastrointestinal complaints - abdominal pain, vomiting and/or constipation
- Polyuria and polydipsia
- Dehydration

BIOCHEMICAL AND LABORATORY DATA

Serum 25-hydroxyvitamin D, otherwise known as 25(OH)D, is considered to be the best index of vitamin D status [53,69,77,78,149,382,391]. Specific points to consider when assessing vitamin D status using serum 25(OH)D include:

- Half-life is documented to be between 2-7 weeks [69,77]
- Levels may fluctuate acutely and ideally should be measured at a time of clinical stability as well as being assessed in conjunction with CRP [392]
- Levels can vary by up to 30% between laboratories [77] and may not be precise [69]
- The 25(OH)D assay must adhere to internationally validated standards [77,149]
- It is unclear whether 25(OH)D levels should be drawn while fasting [77]

Is there an ideal serum 25-hydroxyvitamin D level to aim for in people with CF? PICO8.2.2

[Ungraded] Insufficient evidence specific to CF for the ideal serum 25-hydroxyvitamin D level. It is suggested that the general Australian and New Zealand goal of ≥50 nmol/L[69] be used with a caveat for the time of year at which testing occurs.

There is currently debate in the scientific literature over what constitutes an optimal serum 25-hydroxyvitamin D level, with some CF authorities calling for a target of 75nmol/L and others 50nmol/L. In the general population aiming for serum concentration of 25(OH)D >75 nmol/L is not supported by a significant amount of data from randomised controlled trials [69]. Furthermore there is some evidence of a U-shaped curve when looking at vitamin D and disease outcomes with those who have levels >75 nmol/L (and <30 nmol/L) having greater risk of frailty in women, mortality, schizophrenia and prostate cancers[69].

There is no consensus regarding optimal serum concentration of 25(OH)D to ensure good health in people with CF [77,78,149]. There have also been no studies that have looked at clinical outcomes based on 50 nmol/L versus 75 nmol/L [77]. The CF Foundation recommends maintaining levels above 75nmol/L based on increased fracture rates in the CF population [77] whereas the European Cystic Fibrosis Bone Mineralisation Guidelines [149] and ESPEN-ESPGHAN-ECFS guidelines [78] recommend maintaining levels above 50nmol/L and caution that there is a lack of information on the long term consequences of maintaining vitamin D at levels above 75nmol/L.

Given the lack of any available evidence in the CF literature or otherwise showing improved clinical outcomes with an increased target of 75 nmol/L, it is suggested that the general Australian and NZ goal of ≥50 nmol/L be used, with a caveat for the time of year at which testing occurs.

Is the time of year, specifically the season, important when measuring and interpreting an individual's serum vitamin D level? PICO8.2.3

[Grade C] Aim to measure serum vitamin D at the end of the winter months and adjust supplementation accordingly. If not feasible, take into account the season of assessment when interpreting results and prescribing supplementation. [51,64,65,70-74]

There is a strong body of evidence to support the recommendation of taking serum vitamin D measures at the end of winter or in early spring [51,64,65,70-74]. Vitamin D levels are known to fluctuate throughout the year and levels are lowest in months of less UVB exposure [69,77,78]. Individuals who have sufficient levels at the end of winter are likely to be sufficient for the entire year [77].

If end of winter testing is not feasible, it has been suggested to aim for 10-20 nmol/L above the target of 50 nmol/L at other times of the year to allow for the seasonal decrease in winter [69].

Intervention

ROUTINE SUPPLEMENTATION

While it is known that individuals with pancreatic insufficiency have additional risk factors for poor vitamin D status, the question of whether those with pancreatic sufficiency should be routinely supplemented is difficult to answer at this time. Of eight studies reviewed, five found no significant difference in vitamin D status between pancreatic insufficient and pancreatic sufficient individuals, meaning that both were equally at risk of deficiency [51,64,65,71,72,74-76] and three studies found that those who were pancreatic insufficient were more likely to be deficient [51,64,75]. It is important to note that these studies were retrospective audits, had different definitions of deficiency, often had very small numbers of pancreatic sufficient individuals and were not controlled for season of testing, making a consensus difficult. It does however raise the discussion point that all people with CF regardless of pancreatic status are at risk of deficiency, unlike other fat soluble vitamins where dietary sources and absorption are more relevant.

Should supplemental vitamin D be given to people with pancreatic sufficient cystic fibrosis as part of routine care? PICO8.2.4

[Grade C] There is inconsistent evidence to support routine vitamin D supplementation for all people with CF, regardless of pancreatic status. It is recommended that all people with CF undergo annual serum vitamin D testing and be supplemented accordingly. [51,64,65,71,72,74-76]

What doses of vitamin D are needed to prevent deficiency in people with CF? PICO8.2.5

[Ungraded] There is insufficient evidence available to recommend evidence-based routine supplementation doses for people with CF.

In the general Australian and New Zealand population, the intake target for vitamin D in children, adolescents and adults under 70 years is 600 IU/day if there is minimal sun exposure [387]. However, there are no studies that have looked at the optimal routine dosing of people with CF in order to prevent deficiency. It is therefore recommended that clinicians be guided by the US and European recommendations as outlined in table 8g [77,78].

Table 8g. Recommended routine daily vitamin D supplementation ranges [77,78]

Age group	Recommended range for cholecalciferol dosing (IU)
Infants	400 - 1000
Young children	800 - 2000
Older children, adolescents and adults	800 - 4000

Ergocalciferol and cholecalciferol are the two forms of vitamin D available. Cholecalciferol should be used as it has been shown to be more effective in raising serum 25(OH)D [75,77,78,149]. It is also the major form of supplemental vitamin D currently available in Australia and New Zealand [69]. There are currently no TGA approved parenteral preparations of vitamin D as a single micronutrient.

SUPPLEMENTATION TO CORRECT DEFICIENCIES

Suboptimal vitamin D levels should be treated by giving additional vitamin D as oral supplements and not through phototherapy or sun exposure. Given the high incidence of skin cancer in Australasia, UV radiation avoidance should be taken if the UV index is three or above, especially in the immunosuppressed who are at greater risk of skin cancer [69].

There is no evidence for the frequency of supplementation in people with CF (daily, weekly, monthly etc.) [77]. Large one-off doses of cholecalciferol (STOSS therapy) have been shown to be effective and may overcome the common barrier of adherence [79], however, due to the potential for toxicity this should only be done in conjunction with an endocrinologist with experience in CF. The recommended ranges for vitamin D supplementation doses to correct deficiency are outlined in table 8h below.

What doses of vitamin D are needed to correct deficiency in people with CF? PICO8.2.6

[Grade C] There is a lack of evidence on conventional, daily doses of vitamin D needed to correct vitamin D deficiency.

- Health professionals should be guided by consensus based guidelines[77,78]

There is some evidence to support the use of high dose cholecalciferol ("STOSS therapy") in CF. Use with caution due to risk of toxicity in those who are unable to convert excess cholecalciferol to its inactive form. [79,80]

Table 8h. Recommended daily vitamin D supplementation ranges to correct deficiency [69,77,78,149].

Age group	Recommended cholecalciferol ranges (IU) to correct deficiency
Infants	400 - 2000
Young children	1000 - 5000
Older children, adolescents and adults	1000 - 10 000

Monitoring and Evaluation

Vitamin D status should be assessed at least annually in all people with CF [53,77,78]. It should also be reviewed after initiation of PERT [78] and three months after a change in vitamin D regimen as this is when a steady-state level is reached [53,77,78,387].

Practice Points PICO 8.2.1

There is no evidence to support a causal role between vitamin D and respiratory health, however it is reasonable to assume that individuals with severe lung disease may be more likely to be vitamin D deficient due to spending more time indoors.

Practice Points PICO 8.2.2

It is suggested that the general Australasian goal of ≥50 nmol/L serum 25(OH)D be used if measuring vitamin D at the end of winter or in early spring[69]. If testing at other times of year, aim for a level 10-20nmol/L higher (i.e. ≥60-70nmol/L).

Practice Points PICO 8.2.3

- Aim to measure serum vitamin D at the end of winter/early spring
- Take into account the following when interpreting results:
  - ≥50nmol/L = adequate at the end of winter or in early spring
  - ≥60-70 nmol/L = adequate at other times of the year
- Specific considerations for the Australian and NZ context:
  - Seasonal variations may differ according to geographic location

People from far north of Australia who spend time outdoors during the winter months, may not see as much seasonal variation in serum vitamin D levels

Practice Points PICO 8.2.4

Consider all individuals, including those with pancreatic sufficiency at risk of vitamin D deficiency and screen annually. Supplement as required.

Practice Points PICO 8.2.5

Base routine supplementation of vitamin D on the US and European consensus documents[77,78]:

- Infants = 400-1000 IU
- Young children = 800-2000 IU
- Older children, adolescents and adults = 800-4000 IU

Additional points:

- Take into account medication adherence and cost when prescribing supplementation
- Ergocalciferol and cholecalciferol are the two forms of vitamin D available
- Cholecalciferol should be used as it most effective in increasing serum 25OHD levels.

Cholecalciferol is the major form of supplemental vitamin D currently available in Australia and New Zealand.

Practice Points PICO 8.2.6

Base supplementation of vitamin D to correct deficiency on the US and European consensus documents[77,78]:

- Infants = 400-2000 IU
- Young children = 1000-5000 IU
- Older children, adolescents and adults= 1000-10 000 IU

- Before escalating treatment of vitamin D deficiency, check adherence to PERT and prescribed vitamin supplementation.
- Use of high dose vitamin D supplementation (STOSS) should be carefully evaluated and done in conjunction with an endocrinologist with experience in CF. Some people are unable to convert excess cholecalciferol to its inactive form and are therefore at increased risk of toxicity.

Refer to an endocrinologist if people are unresponsive to maximal treatment doses.

Translating Into Practice - Conversions

- 1 IU vitamin D = 0.025 µg cholecalciferol
  - 0.005 µg 25(OH)D
- 1 µg vitamin D = 40 IU cholecalciferol
  - 200 IU 25(OH)D

8.3 Vitamin E

J. Anderson

Vitamin E is made up of eight fat soluble compounds. Naturally occurring vitamin E, *d-* (or *RRR*) alpha (α)-tocopherol, is the most biologically active form. It functions primarily as an antioxidant to protect polyunsaturated fatty acids from oxidation [43,359,393]. Dietary sources of vitamin E include vegetable oils, nuts, seeds, wholegrain breads and cereals, green leafy vegetables, fish, seafood, meat and poultry [43].

Disease Aetiology

VITAMIN E DEFICIENCY

In addition to the factors contributing to fat soluble vitamin deficiency in CF, as outlined in figure 8a, vitamin E deficiency in CF may result from high levels of oxidative stress and consequently increased antioxidant requirements [281,362,368]. Pancreatic sufficient people with CF may also be at risk of vitamin E deficiency [1,394].

Historically, symptoms reflective of severe vitamin E deficiency in CF have been reported, including peripheral neuropathy, ataxia and haemolytic anaemia [395-398]. However overt clinical symptoms due to vitamin E deficiency are now considered rare in people with CF [365]. More recently, cognitive deficits have been described post prolonged periods of vitamin E deficiency during infancy [83].

Subclinical vitamin E deficiency as indicated by low serum α-tocopherol is reported as being relatively common in CF:

- Infants: up to 45% of newly diagnosed infants present with vitamin E deficiency [47,71,83]
- Children and adults: 15-55% of children and adults are vitamin E deficient[51,52,81,85]

The clinical significance of subclinical deficiencies and improvements with vitamin E supplementation remain unclear, however positive associations have been shown between vitamin E supplementation and the following:

- Pulmonary function [52,54]
- Markers of oxidative stress [48,399]
- Cognitive function in infants [83,84]

Suboptimal vitamin E levels are more prevalent in individuals who are pancreatic insufficient [49,51,52,85].

VITAMIN E TOXICITY

No evidence of overt vitamin E toxicity has been reported in CF and deficiency remains the major concern [365]. There is some evidence in non-CF populations that excessive vitamin E may antagonise vitamin K absorption and/or function [400].

Assessment

DIET

Dietary sources of vitamin E, as outlined in Table 8i below, should be considered with attention given to intake of polyunsaturated fatty acids in food, oral and enteral nutrition support and supplements. Vitamin E requirements are known to increase with an increase of polyunsaturated fatty acid consumption in the diet [48,401]. Whilst most dietary sources of polyunsaturated fatty acids are relatively rich in vitamin E, supplements such as fish oils, do not provide the extra amount of vitamin E needed. Attention should be given to patients limiting fat intake to control fat malabsorption as this may increase the risk of vitamin E deficiency.

Table 8i. Vitamin E containing foods [376]

	Serving size	Vitamin E (mg) per serve	Vitamin E (mg) per 100g
Fats and Oils			
Sunflower	1tsp	2.4	51
Olive	1tsp	0.9	20
Peanut	1tsp	0.6	12.5
Margarine (polyunsaturated)	1tsp	0.4	8.0
Butter	1tsp	0.5	9.9
Nuts, Seeds & Legumes			
Sesame seeds	1tsp	5.4	193
Sunflower seed	1tsp	0.4	39
Almonds	10 nuts	2.9	24
Peanuts	10 nuts	0.9	10.1
Peanut butter	1tsp	0.5	8.5
Soya beans	1 cup	3.2	1.7
Lentils	1 cup	0.74	0.4
Breads and Cereals			
Wheat germ	¼ cup	5.7	22.6
Wholemeal flour	1 cup	2.8	2.0
Bran cereal	1 cup	1.2	1.9
Rolled oats	1 cup	1.3	1.6

...table continued overleaf

	Serving size	Vitamin E (mg) per serve	Vitamin E (mg) per 100g
Animal-based sources			
Salmon (cooked)	100g	3.2	3.2
Beef (cooked)	100g	1.3	1.3
Chicken thigh cooked	100g	0.6	0.6
Fruits and Vegetables			
Olives	4 olives	1.1	7.2
Sweet Potato, raw	1 medium 420g	19.3	4.6
Capsicum, raw	1 small 220g	9.5	4.3
Eggplant, raw	1 small 318g	9.5	3.0
Spinach, raw	1 cup	0.8	1.7
Peaches	1 cup sliced	2.1	1.3
Carrots, raw	1 medium 130g	1.0	0.8
Tomatoes	1 small 120g	1.0	0.8
Lettuce	1 cup	0.4	0.8

CLINICAL

Signs and symptoms of vitamin E deficiency include [43,84,365]:

- Fatigue
- Spinocerebellar ataxia
- Peripheral neuropathy
- Skeletal myopathy
- Haemolytic anaemias
- Retinal defects
- Cognitive impairment

Whilst rare, vitamin E toxicity is likely to present in a similar fashion to that of deficiency [363].

BIOCHEMICAL AND LABORATORY DATA

How should vitamin E levels be assessed for people with CF? PICO 8.3.1

[Ungraded] There is insufficient evidence to make a CF-specific recommendation. Serum α-tocopherol is the most common measure used to assess vitamin E status in people with CF. However there is significant variability in what is used to define deficiency, adequacy and excess. In the absence of evidence health professionals should continue to use serum α-tocopherol when assessing vitamin E status. Lipid adjustment may provide a more accurate assessment of vitamin E status and may be considered where available.

Serum or plasma α-tocopherol is the most common measure used to assess vitamin E status for the general and CF population. Variation exists in standard reference ranges for vitamin E adequacy [365], so interpret results using reference ranges provided by the laboratory doing the test.

There is some limited evidence to suggest that higher vitamin E target serum levels may be required for those with CF to meet oxidative stress requirements [82] and to optimise pulmonary function [52,54].

Vitamin E circulates in the blood bound to lipoproteins. Lipid adjustment is therefore often recommended for a more accurate measurement of vitamin E levels [82,363,365,367,402]. Options include:

- α-tocopherol to total lipid (cholesterol, triacylglycerol and phospholipid) ratio [365,402,403]:
    - Normal ratio in children = 0.6mg/g
    - Normal ratio in adults = > 0.8mg/g
        - This test is not routinely available in the clinical setting
- α-tocopherol to cholesterol ratio [285,359,402]:

This is recommended only when total lipid content is not available as it is not as sensitive a marker.

- General population (lower limit normal) = 2.47mg/g
- CF population (suggested lower limit normal) = 5.4mg/g [78,82]

Points to consider when using lipid adjustment ratios in the assessment of vitamin E status:

- People with CF typically have lower serum cholesterol levels than the reference population and low serum α-tocopherol levels may be a reflection of low lipid levels rather than low vitamin E status. The serum α-tocopherol to total lipid ratio may be in the normal range [365,404].

There is no consensus as to whether patients should be fasted for the assessment of Vitamin E. In practice, vitamins A and E are usually measured using the same assay and therefore practically both are measured using the same protocol [380]. Ideally lipid ratios should be assessed in a fasting state.

Intervention

What is the role for supplementation of vitamin E in people with CF? PICO 8.3.2

[Grade C] Routinely supplement vitamin E in people with CF who are pancreatic insufficient.

For pancreatic sufficient individuals commence supplementation on an individual basis.

There is inadequate evidence to establish recommendations for supplement dose specifically for CF. Overall the evidence is insufficient to recommend change from current practice as per the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*' (Table 8j).[1 47-54,81-86]

Table 8j outlines recommended vitamin E supplement doses, according to the *2006 Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis* [1]. These recommendations are in line with the most recent European recommendations [78]. Refer to the Nutrient Reference Values for Australia & New Zealand webpage for the vitamin E as α-tocopherol equivalents (TE), adequate intake (AI) values for the general population [43].

Table 8j. Recommended daily starting doses of vitamin E supplementation for pancreatic insufficient people with CF [1] (1mg *d*- (*RRR*) α-tocopherol = 1.5IU, 1mg *dl*-(*all-rac*) α-tocopherol = 1.0IU)

Age	Recommended Vitamin E supplementation (IU)
Infants	40-80
Young children	50-150
Older children	150-300
Adolescents and adults	150-500

The upper limits of these supplementation ranges are similar to age-specific recommended upper limits of intakes for the general population in Australia and NZ [43].

What is the safe upper limit for vitamin E supplementation for people with CF? PICO 8.3.3

[Ungraded] There is insufficient evidence available regarding the safe upper limit for vitamin E supplementation in CF. Health professionals should be guided by the upper limit of the age-specific supplementation ranges recommended in the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*' for routine supplementation of vitamin E (table 8j)[1]. Make a thorough assessment of risks and benefits before considering higher supplement doses as required to correct deficiency states, and closely monitor the response to supplementation.

A safe upper limit has not yet been determined for people with CF. Two studies report high serum vitamin E levels with varying supplementation regimens, with neither study identifying an association between vitamin E intake and reports of adverse effects [82,86]. In the general healthy population, high dose vitamin E supplementation at intakes well above recommended daily requirements had been considered to have few adverse effects [43,405]. However recent results from a large randomised clinical trial [406] show that supplementation with synthetic vitamin E 400 IU/day may harm adult men older than 50 years in the general population, by increasing the risk of prostate cancer. It is therefore recommended that patients are supplemented within the ranges recommend in Table 8j. Supplementation in doses above these ranges should only be considered following a thorough assessment of risks and benefits on an individual basis.

Monitoring and Evaluation

How often should vitamin E levels be measured in people with CF? PICO 8.3.4

[Ungraded] Insufficient evidence to make a recommendation. Health professionals should continue to follow recommendations in the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*', to assess annually and to monitor more frequently in those at high risk of deficiency or toxicity[1].

There is currently no evidence available to inform practice about the optimal frequency of vitamin E monitoring. In line with the previous version of this guideline, it is suggested that vitamin E status is monitored in all people with CF at diagnosis and then at least annually [1]. More frequent monitoring may be required in the following circumstances [1,78]:

- Presence of CF-related liver disease or intestinal resections
- Recent changes in vitamin E supplementation regimens

Adherence to PERT and vitamin supplementation should also be considered at each nutritional review

Practice Points PICO 8.3.1

Serum or plasma levels of α-tocopherol are the most common measure used to assess vitamin E status. However there is significant variability in what is used to define deficiency, adequacy and excess.

- Interpret results using reference ranges provided by the laboratory doing the test.

Measurement of α-tocopherol to total lipid ratio will aid in the interpretation of serum vitamin E status in the following situations:

- Abnormal serum α-tocopherol levels
- Abnormal lipid levels (common in CF and liver disease)
    - Normal ratio in children = 0.6mg/g
    - Normal ratio in adults = > 0.8mg/g

When not available, the α-tocopherol to cholesterol ratio can be used in place of total lipid ratio although;

- Overall a less sensitive and specific test
- Aim for a ratio >5.4mg/g in CF
- Where possible measure fasting levels of total lipid ratios.

There is no evidence for the assessment of other tocopherols including γ-tocopherol in CF.

Practice Points PICO 8.3.2

Routine supplementation of vitamin E is recommended for all pancreatic insufficient people with CF. Aim to achieve the normal population reference ranges. At this time, continue to follow the *'2006 Australasian Clinical Practice Guidelines for Nutrition in CF'* when supplementing vitamin E in CF[1]:

- Infants: 40 - 80IU/day
- Children 1 to 3 years: 50 - 150IU/day
- Children 4 to 7 years: 150 - 300IU/day
- Children > 8 years & Adults: 300 - 500IU/day

Consider supplementation on an individual basis for the pancreatic sufficient population.

Higher supplementation doses may be required if significantly increased dietary and/or supplemental polyunsaturated fatty intakes.

- If ongoing deficiency despite recommended levels of supplementation, consider adherence to prescribed supplement and PERT before increasing the dose further.

Water-miscible vitamin E preparations are generally more bioavailable than fat soluble preparations.

Practice Points PICO 8.3.3

A safe upper limit has not yet been determined for vitamin E supplementation in CF.

No evidence of vitamin E toxicity in CF. Supplementation above the upper recommended dose should only be considered following thorough dietary and clinical assessment and based on serum levels.

Practice Points PICO 8.3.4

Assess vitamin E status annually.

Monitor more frequently in the following groups:

- Infants: 2 months post first commencing supplementation [87]
- After changing supplementation doses i.e. 3-6 months post changes
- After changes to treatment for malabsorption where a change in the level of fat absorption has occurred.
- People with CF-related liver disease or history of intestinal resection or malabsorption

People with poor adherence to PERT and fat soluble vitamin supplementation

Translating into Practice

- The naturally occurring form of vitamin E is *d*-(or RRR) α-tocopherol
- Vitamin E activity is traditionally expressed in terms of equivalents of this isomer (mg alpha- tocopherol equivalents or α-TE)
- Synthetic forms of vitamin E are referred to as *dl*-(or all-rac) α-tocopherol
- Naturally occurring vitamin E is more biologically active than the synthetic form. However, it is also more expensive. Therefore, in Australia and New Zealand, supplements may contain either *d*-α-tocopherol or *dl*-α-tocopherol, as well as other less active forms of vitamin E (e.g. gamma (γ)-tocopherol).

Lipid Ratios

The calculation of the vitamin E to cholesterol ratio requires the conversion of units to mg/g to enable the comparison to suggested reference ranges. This will require the conversion of *α-tocopherol from µmol/ to mg/L and the conversion of total cholesterol from mmol/L to g/L. Then divide α-tocopherol mg/L by cholesterol g/L to get the ra*tio.

E.g. Patient with *α-tocopherol 7.0umol/L and total cholesterol 3.5mmol/L*

- *α-tocopherol: 1µmol/L = 0.43mg/L*
  - 7.0µmol/L x 0.43 = 3.01mg/L
- Cholesterol: 1mmol/L = 386.65mg/L = 0.389g/L
  - 3.5mmol/L x 0.386 = 1.365g/L
- For ratio: divide α-tocopherol mg/L by cholesterol g/L
  - 3.01/1.365 = 2.2mg/g

Recommended lower limit for general population is 2.47mg/g so this patient is likely vitamin E deficient

Conversions

- Converting *d*-(or *RRR*) α-tocopherol between mg and IU
  - 1mg = 1.5IU
  - 1IU = 0.67mg
- Converting *dl*-(or *all-rac*) α-tocopherol acetate between mg and IU
  - 1mg = 1IU
  - 1IU = 1mg
- Converting *dl*-(or *all-rac*) α-tocopherol between mg and IU
  - 1.1mg = 1IU
  - 0.91IU = 1mg

Note: *dl*-(or all-rac) α-tocopherol and *dl*-(or all-rac) α-tocopherol acetate are both used in supplements. Vitamin E status is usually measured as serum α-tocopherol and reported as umol/L. However units of measurements differ internationally. Converting α-tocopherol:

- 1 ug/dL = 0.023umol/L
- 1 umol/L = 0.43mg/L

8.4 Vitamin K

J. Anderson & S. King

Vitamin K consists of a group of essential fat soluble compounds [407]:

- Phylloquinone (Vitamin K_1)
- Menaquinones – over 10 forms (Mk-n – Vitamin K_2)

Vitamin K is an essential cofactor for the activation of coagulation proteins such as prothrombin and bone related proteins such as osteocalcin [43,92,365]. Deficiency has been implicated in defective bone mineralisation in the general population and people with CF [360].

Vitamin K_1 is found in the diet in dark green leafy vegetables such as spinach, broccoli, cabbage and kale. Vegetable oils including canola, soybean and to a lesser extent olive oil are also rich sources [43]. Vitamin K_2 is synthesised mostly by gram-positive bacteria in the jejunum and ileum [43,408].

Disease Aetiology

VITAMIN K DEFICIENCY

In addition to the factors contributing to fat soluble vitamin deficiency in CF, as outlined in figure 8a, vitamin K deficiency in CF may result from:

- Chronic antibiotic use, malnutrition and small bowel bacterial overgrowth
  - May potentially reduce gut microbiota synthesis of vitamin K, though it is unclear how much this contributes to vitamin K status [359,409]
- Chronic steroid administration [360]
- Excessive vitamin E may antagonise vitamin K absorption and/or function [43 400].

Overt vitamin K deficiency presenting with coagulation disorders is now rare in patients with CF, however sporadic cases are still reported in the literature [359]. Conversely, subclinical vitamin K deficiency is common in patients with pancreatic insufficiency, both with and without vitamin K supplementation [88,91,92,95]. However subclinical vitamin K deficiency may be under-recognised in clinical practice, given the difficulties in accurately assessing vitamin K status. Whilst the relevance of subclinical vitamin K deficiency in people with CF remains unclear, it has been associated with abnormal biomarkers of bone and decreased bone mass [90,93-95,359,408].

VITAMIN K TOXICITY

There are no reported adverse events or toxicity associated with consumption of vitamin K as food or supplements. Similarly, no adverse effects have been reported at any dosage level of vitamin K in patients with CF [202]. Vitamin K is considered to have a wide safety margin [408].

Assessment

DIET

Dietary sources of vitamin K should be considered taking into account that dietary intake of vitamin K varies considerably. Also, the assessment of reported intake is limited by the lack of comprehensive vitamin K content in food composition databases [407]. There is no Australian/NZ food composition data for vitamin K. As part of a thorough nutrition assessment, vitamin K intake from enteral nutrition and prophylactic supplements should also be considered. The overall absorption from dietary sources (plant and plant oils) appears to be no more than 20% of that from a supplement [43]. Dietary sources of vitamin K are outlined in table 8k.

Table 8k. Vitamin K containing foods [410]

	Serving size	Serving size	Vitamin K content (mg) Per serve
Fruits and Vegetables			
Parsley	2g pinch	0.013	1.64
Swiss Chard, raw	1 cup	0.37	0.83
Kale, raw	1 cup	0.80	0.70
Spinach, raw	1 cup	0.21	0.48
Radicchio	1 cup	0.27	0.55
Watercress	1 cup	0.16	0.50
Coriander, Raw	2g pinch	0.006	0.31
Spring Onion, raw	1 onion	0.03	0.20
Brussels Sprouts	4 sprouts	0.13	0.17
Lettuce, Raw	1 cup	0.06	0.12
Rocket, Raw	1 cup	0.064	0.11
Broccoli, Raw	4 florets	0.08	0.10
Cabbage, Savoy, Raw	1 cup	0.08	0.07
Fats & oils			
Vegetable Oil Margarine	1tsp	0.004	0.10
Canola Oil	1tsp	0.003	0.07
Olive Oil	1tsp	0.003	0.06

CLINICAL

In addition to dietary sources (food and supplements), consider the following when assessing vitamin K status and the risk of deficiency:

- Adherence to recommended supplementation and PERT
- Chronic use of antibiotics and/or steroids.

Signs and symptoms of overt vitamin K deficiency including [365]:

- Easy bruising or excessive bleeding

While the physiological implications of subclinical vitamin K deficiency remain unclear, it is suggested that the vitamin K status of people with CF who have low bone mineralisation density is reviewed [360].

BIOCHEMICAL AND LABORATORY DATA

How should vitamin K status be assessed for people with CF? PICO 8.4.1

[Ungraded] There is insufficient evidence to make a recommendation about methods for assessing vitamin K status.

At this time, it is recommended that health professionals assess vitamin K status using the best readily available biochemical measure together with a thorough diet and clinical assessment.

There is no readily available universally accepted, single robust biomarker or measure of vitamin K status (sufficiency or deficiency) [78,400]. Serum vitamin K is unreliable and should not be used to assess vitamin K status in CF [202,408,411]. The following alternatives are available:

- PIVKA-II (protein induced vitamin K absence-II) and uc-OC (undercarboxylated osteocalcin) are considered the most accurate measures of vitamin K status [365,408].
    - PIVKA-II is a relatively sensitive measure of detecting vitamin K deficiency of the liver [365,408].
    - uc-OC is the most sensitive indicator of vitamin K status of the bone and is the most sensitive indicator of overall vitamin K status [408].
- Both PIVKA-II and uc-OC are not readily available in clinical practice and are currently used mainly in research. Measure of coagulation - Prothrombin Time (PT) is typically used as a surrogate measure of vitamin K status.
    - PT is an insensitive and non-specific test of vitamin K deficiency.
    - A prolonged PT is a marker of advanced vitamin K deficiency [149].
    - Liver stores of vitamin K will be severely depleted with a prolonged PT [365,408].
    - PT requires a large amount of blood in infants. Not recommended as a test except in infants with CF-related liver disease [87]

See Chapter 11 for vitamin K assessment in CF-related liver disease.

Intervention

Should vitamin K supplementation be recommended for all people with CF and pancreatic insufficiency?
PICO 8.4.2

[Grade C] Routinely supplement vitamin K in all people with CF and pancreatic insufficiency as outlined in table 8l. In practice supplementing at these doses will require an increase in vitamin K supplementation doses that are routinely provided and currently available in Australia and NZ.

There is insufficient high quality evidence available to recommend an optimal dose. [85,88-95]

Since the release of the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*' [1], there has been an increase in the vitamin K supplementation doses recommended in international consensus documents, based largely on recent evidence indicating the important role of vitamin K in bone health [407,409]. It is therefore recommended that health professionals look to the most recent 2016 European guidelines [78] for guidance until a consensus in Australia and New Zealand is achieved.

Table 8l. Recommended daily starting doses of vitamin K supplementation for pancreatic insufficient people with CF according to the ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children and adults with cystic fibrosis [78].

Age	Recommended vitamin K supplementation (µg)
Infants	300 - 1000
Children, adolescents and adults	1000 – 10 000

Refer to the following documents for more information:

- 2011 European Cystic Fibrosis Bone Mineralisation Guidelines [149]
    - Higher recommendation for infants 0-12 months (500-2000µg/d)
    - Supplementation should be considered for infants at increased risk of vitamin K deficiency
- Nutrient Reference Values for Australia & New Zealand webpage http://www.nrv.gov.au/[43]
    - Vitamin K adequate intake (AI) values for the general population
    - No upper limit of intake has been set

Consider supplementation on an individual basis for the pancreatic sufficient population. Commence supplementation when low levels are detected or when clinically indicated [149].

Consider the following regarding vitamin K supplementation in CF:

- For the past 20 years, prophylactic vitamin K has been given to all newborns in Australia and New Zealand at birth [360].
- Routine supplementation of vitamin K is usually provided as part of a CF-specific multivitamin for infants, children and adults, however in amounts below recommended supplementation doses.
- Vitamin K has a rapid metabolic turnover and the body has limited stores. Suggest daily rather than weekly supplementation of vitamin K [149,285].
- Routine supplementation should continue despite difficulties in accurately monitoring blood levels in most clinical environments [408].
- Attention should be given to patients with chronic antibiotic use due to increased risk of vitamin K deficiency [360]. Higher doses may be required for these patients [78,360].

See Chapter 11 for vitamin K supplementation in CF-related liver disease

Monitoring and Evaluation

How often should vitamin K levels be measured in people with CF? PICO8.4.3

[Ungraded] Insufficient evidence to make a recommendation. Aim to assess vitamin K status at diagnosis and annually in all people with CF.

As per recommendations for other fat soluble vitamins, clinicians should aim to assess vitamin K status at diagnosis and annually in all people with CF. More frequent monitoring may be required in the following circumstances [1,78]:

- Presence of CF-related liver disease or intestinal resections with severe malabsorption
- Haemoptysis or haematemesis
- On broad spectrum antibiotic regimens

Ideally vitamin K status should be re-checked 3 to 6 months after any change to vitamin K supplementation and treatment for malabsorption. Adherence to pancreatic enzyme replacement therapy and vitamin supplementation should also be considered at each nutritional review.

Practice Points PICO 8.4.1

- There is no readily available direct measure of vitamin K status (sufficiency or deficiency).
- Serum vitamin K is unreliable and should not be used to assess vitamin K status in CF.
- PIVKA-II (protein induced vitamin K absence-II) and uc-OC (undercarboxylated osteocalcin) are considered the most accurate measures of vitamin K status.
  - Not readily available in clinical practice in Australia and New Zealand
- Prothrombin Time (PT) is a measure of coagulation and is often used as a more readily available surrogate measure of vitamin K status. Consider the following prior to use:
  - Insensitive and non-specific
  - Marker of advanced vitamin K deficiency.
  - Not recommended in infants, other than those with CF-related liver disease as it requires large amount of blood for collection

Ideally assess biochemical status using a more accurate measure such as PIVKA-II, however where not available, use surrogate measure of PT.

Practice Points PICO 8.4.2

Vitamin K supplementation is recommended for all pancreatic insufficient people with CF. At this time, it is recommended to follow the most recently released international guidelines for vitamin K supplementation dosing in CF.

- *ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children and adults with cystic fibrosis*[78]
  - Infants: 300 - 1000µg
  - Children & Adults: 1000 – 10 000 µg

Higher doses may be required for those with CF-related liver disease, intestinal resection or when on longer term antibiotic or steroid regimens.

Daily administration of vitamin K is preferred due to the body's low storage capacity.

Vitamin K preparations in Australia and New Zealand all contain vitamin K1 (phytomenadione), however in amounts well below recommended supplementation doses.

Additional supplementation of vitamin K may be required particularly for those considered at high risk of deficiency and/or with bone disease, however, evaluate the availability, cost and treatment burden for people with CF.

Practice Points PICO 8.4.3

Aim to assess vitamin K status annually.

- Additional screening for vitamin K deficiency should be considered for newly diagnosed patients and those with haemoptysis/haematemesis, CF-related liver disease or recent intestinal resection.

Vitamin K status should ideally be re-checked 3 months after any change to vitamin K supplementation or treatment for malabsorption.

CHAPTER 9 MINERALS

A. Kench, J. Grunert, J. Heyward & J. Anderson

As part of a comprehensive nutrition review, both macro- and micronutrients (vitamins and minerals) are assessed in CF. This chapter will cover the key minerals that are considered to be at risk of deficiency for people with CF.

9.1 Iron

Iron status is often compromised in adults and children with CF [96,412-415]. Iron is a component of haemoglobin, which circulates in the blood via erythrocytes (red blood cells) and is responsible for the transport of oxygen around the body [43]. It is also found in readily metabolised body stores as ferritin, in the muscle as myoglobin, and in a variety of enzymes used for metabolic processes including oxygen and electron transport [43]. Iron is found in animal and plant-based food sources. Meat, fish and poultry provide good amounts of dietary iron. Less biologically available plant-based sources include wholegrain cereals and leafy green vegetables.

Disease Aetiology

Anaemia is defined as a deficiency in haemoglobin or the number of circulating red blood cells. Iron deficiency is the most common form of anaemia [416]. Iron deficiency is usually classified as absolute or functional iron deficiency [417].

ABSOLUTE IRON DEFICIENCY

- Iron stores are depleted and thus unavailable for erythropoiesis [417]

FUNCTIONAL IRON DEFICIENCY (ANAEMIA OF CHRONIC DISEASE OR INFLAMMATION)

- Iron stores are adequate or even higher than normal but there is insufficient iron available at the site of erythroblast production [417].

It is thought that both absolute and functional iron deficiency play a role in the pathophysiology of iron deficiency in the paediatric CF population [415]. Functional iron deficiency is the primary cause of iron deficiency in the adult CF population [96,412-414].

Iron deficiency usually occurs after a period where losses or requirements exceed intake and/or absorption of iron [418]. Iron deficiency is therefore more common in the following populations, with or without CF [418]:

- The paediatric population, especially during periods of rapid growth
- Pregnant, breastfeeding and menstruating women
- Endurance athletes
- Blood donors

The following factors also contribute to iron deficiency, especially in the CF population [415,419,420]:

- Chronic inflammation
- Inadequate dietary intake - particularly for people following a vegetarian or vegan diet
- Gastrointestinal co-morbidities – malabsorption, small intestinal bacterial overgrowth or gastro-oesophageal reflux (GOR)
- Haemoptysis
- Chronic bacterial colonisation of the airways

Although a direct causal relationship has not been established, it has also been suggested that chronic colonisation by Pseudomonas aeruginosa (PA) may cause iron deficiency in CF due to:

- PA using extracellular iron for growth [421]
- PA stimulating the production of cytokines, diverting iron from haemoglobin synthesis and in turn promoting local iron storage in the airways of people with CF [420]

The prevalence of iron deficiency in children with CF has been reported to be 17-33% [415,419,422], increasing to >60% in the adult CF population [414,419,422].

Assessment

When assessing iron status for a person with CF, it is important to consider the following:

- Adequacy of dietary iron intake
- Clinical indicators of potential iron deficiency
- The underlying cause of iron deficiency
- Biochemical markers for iron status

DIET

Normal iron absorption is known to vary from 10% or less in iron-fortified infant cereals, to 50% in breast milk [43]. On average, less than 20% of the iron available in the western diet is absorbed [418]. The following factors are thought to contribute to the proportion of iron absorbed from food [43]:

- An individual's iron status
- The overall iron content of foods consumed
- Type of iron consumed (haem vs. non-haem iron)
    - Haem iron is found primarily in meat, seafood and poultry and is more bioavailable than non-haem iron. In the western population, haem iron contributes to 10-15% of total iron intake [423].
    - Non-haem iron is less bioavailable than haem iron and is present in both animal (meat, seafood and poultry) and plant-based food sources (wholegrain cereals and green leafy vegetables) as well as iron-fortified foods.
- The impact of other nutrients on the absorption of iron
    - Vitamin C and organic acids such as citric, lactic or malic acid as well as the consumption of meat, fish and poultry can enhance the absorption of non-haem iron.
    - Calcium, phytates (found in legumes, rice and other grains) and tannins (found in tea) can inhibit the absorption of haem and non-haem iron.

Wholegrain cereals, meats, fish and poultry are the major contributors to iron intake in Australia and New Zealand [43], see Table 9b. Iron requirements for the general Australian and New Zealand population are outlined in Table 9a.

Table 9a. Recommended Dietary Intake (RDI) of iron for people in Australia and NZ, mg/day [43].
Available at: http://www.nrv.gov.au/

Recommended Dietary Intake (RDI) for Iron		
	Males (mg/day)	**Females** (mg/day)
Infants		
0-6 months	0.2	0.2
7-12 months	11	11
Young children		
1-3 years	9	9
4-8 years	10	10
Children & adolescents		
9-13 years	8	8
14-18 years	11	15
Adults		
19-30 years	8	18
31-50 years	8	18
51-70 years	8	8
<70 years	8	8

Table 9b. Iron containing foods (mg per serve) [424]

	Serving Size	Iron (mg)	mg/100g
Animal-based iron sources			
Chicken liver	100 g	11	11
Beef	100 g	3.5	3.5
Kangaroo	100 g	3.2	3.2
Lamb	100 g	2.5	2.5
Salmon	100 g	1.3	1.3
Tinned tuna	100 g	1.1	1.1
Pork	100 g	0.8	0.8
Chicken	100 g	0.4	0.4
Snapper	100 g	0.3	0.3
Plant-based iron sources			
Weet-Bix™	30 g	4.2	14
All Bran™	30 g	3.2	10.7
Kidney beans	1 cup	3.1	2.1
Green lentils	1 cup	3	6.8
Tofu	100 g	3	3
Chickpeas	1 cup	2.7	1.8
Cooked wholemeal pasta	1 cup	2.3	1.8
Cashew nuts	20 nuts	1.5	5
Raw spinach	1 cup	1.2	3.2
Rolled oats	30 g	1.1	3.7
Almonds	30 g	1.1	3.7
Dried apricots	5 apricots	0.9	3.1
Broccoli	1 cup	0.9	0.8
Cooked brown rice	1 cup	0.7	0.5

DIETARY CONSIDERATIONS FOR INFANTS

- The bioavailability of iron in breast milk is high although not enough to meet the iron requirements for infants greater than 6 months in age. Iron-rich foods, including iron-fortified cereals and pureed meats should also be included at the time of introduction of solids [425].
- Cow's milk is low in iron and as a result, should not be recommended as the main drink for infants less than 12 months of age [425]. The excess consumption of cow's milk, replacing iron-rich food sources, should also be considered as a potential cause of iron deficiency in toddlers.

CLINICAL

Symptoms of iron deficiency may include [43,418]:

- Reduced physical work capacity and fatigue
- Delayed psychomotor development in infants
- Impaired cognitive function
- Impaired immunity
- Adverse pregnancy outcomes
- Faltering growth during infancy

In addition to the factors contributing to potential iron deficiency in CF *(as outlined in disease aetiology)*, the following should also be considered as potential underlying causes [418]:

- Gastrointestinal conditions – cow's milk protein allergy, coeliac disease, gastrointestinal blood losses
- Parasitic infections

BIOCHEMICAL AND LABORATORY DATA

Anaemia is defined as serum haemoglobin (Hb) levels below the reference range for age and gender [418]. However, anaemia is not always a result of iron deficiency. A corresponding low mean corpuscular volume (MCV) or mean corpuscular haemoglobin (MCH) usually indicates anaemia resulting from iron deficiency [418].

If iron deficiency is suspected, further testing of iron studies, including serum iron, transferrin, transferrin saturation, ferritin +/- soluble transferrin receptor (sTfR) should be requested [418]. Overall serum ferritin, which reflects the size of the iron store, is most commonly used to assess iron status in the general population [426]. However, serum ferritin is also an acute phase protein and is elevated during periods of inflammation. Care should be taken when interpreting biochemical markers of iron status in conditions that are complicated by chronic inflammation, as is often the case in CF, as serum ferritin levels may be within normal limits or falsely elevated when iron stores are low [96]. A summary of the biochemical markers used to assess iron status and their interpretation is outlined in Table 9c.

Table 9c. Interpretation of biochemical markers used to assess iron status in the general population*

Diagnosis	Haemoglobin (Hb)	Mean cell volume (MCV)	Serum ferritin (µg/L)	Transferrin or total iron binding capacity	Transferrin saturation	Soluble transferrin receptor (sTfR)	Serum iron
Iron deficiency	Normal	Normal (or low)	Low	Normal to High	Low to Normal	Normal to High	Low
Iron deficiency anaemia (absolute)	Low	Low	Low	High	Low	High	Low
Anaemia of chronic disease or inflammation	Low	Normal	Normal to High	Normal	Low	Normal	Low
Iron deficiency anaemia with chronic disease (functional)	Low	Low	Low to Normal	Normal to High	Low	High	Low

*Adapted with permission from Parischa et al. [418]

How should iron status be assessed in people with CF? PICO 9.1.1

[Grade C] The level of evidence to guide practice for assessing iron status in CF is insufficient. Further research or expert consensus is required. Until further evidence is available, it is suggested that iron status in CF be assessed as per guidelines for the general population. [96,97]

Intervention

How should iron deficiency be treated in people with CF? PICO 9.1.2

[Ungraded] There is insufficient evidence available regarding the treatment of iron deficiency in CF.

Key points to consider in the treatment of iron deficiency:

- Increasing dietary iron intake alone is often inadequate in the treatment of iron deficiency [418]. However, dietary iron intake should still be optimised and the impact of iron enhancers and inhibitors on absorption should be considered.
- Treatment of iron deficiency should depend on the underlying cause.

Absolute iron deficiency: A prescribed iron supplement is usually required. Available preparations in Australia and NZ can be found in Table 9d [412,415,420].

- If a prescription supplement is required, suggested oral treatment doses [418]:
  - Children: 3-6mg/kg/d elemental iron for 2-3 months after serum Hb normalises
  - Adolescents & adults: 100-200mg elemental iron daily for 3-6 months after serum Hb normalises
- Intravenous (IV) supplementation may be required for some patients who do not respond to oral treatment[418].

Functional iron deficiency: Aim to treat the underlying source of inflammation. A prescribed iron supplement is not always required [412,415,420].

Table 9d. Readily available iron supplements in Australia

	Preparation	Dose	Elemental iron (mg)
Ferro-Gradumet ®	Tablet	1	105
Ferrograd C®	Tablet	1	105
Ferro-Liquid ®	Liquid	5ml	30

Refer to http://www.pharmac.govt.nz/Schedule for a list of current iron supplements available in New Zealand.

Is iron supplementation contraindicated in people with CF who are chronically colonised with Pseudomonas aeruginosa? PICO 9.1.3

[Grade D] There is insufficient evidence from clinical trials to suggest that iron supplementation is contraindicated in adults and children with CF who are chronically colonised with Pseudomonas aeruginosa. When indicated, an iron supplement should be prescribed for adults and children with CF who are chronically colonised with pseudomonas aeruginosa. [98]

Monitoring and Evaluation

It is recommended that iron status be assessed annually in the CF population [78]. If iron deficiency is suspected, then the frequency of monitoring should increase [78]. If oral iron supplementation is required, the recommended duration of treatment will depend on the severity of iron deficiency at diagnosis. After commencing oral supplementation at the prescribed therapeutic dose, it is expected that reticulocytosis will occur within the first few days [418,427]. Haemoglobin (Hb) levels are then expected to rise by approximately 20g/L every few weeks [418]. Iron stores should be restored within 2-3 months of Hb stabilisation in the paediatric population and 3-6 months in the adult population [418,427].

The following should be considered when reviewing patients with iron deficiency:

- Tolerability of supplementation - nausea, epigastric pain and constipation are common side effects of prescribed iron supplements [427].
- Adherence to supplementation - poor adherence to iron supplementation is common, especially due to the above gastrointestinal side effects [418,427].

Iron studies should be repeated at the end of treatment to ensure that iron deficiency has resolved.

Practice Points PICO 9.1.1, 9.1.2 and 9.1.3

Increased risk of iron deficiency in CF due to chronic inflammation, inadequate dietary intake, gastrointestinal comorbidities and haemoptysis. Iron studies are difficult to interpret in CF due to chronic inflammation. Aim to assess iron status during clinical stability.

Interpretation of biochemical markers in CF - Serum ferritin is an acute phase protein (rises during periods of inflammation) and may be unreliable. Inflammatory markers, including C-reactive protein (CRP) should be taken into consideration.

- Serum transferrin receptor (sTfr) is not readily available but should be considered as it is not affected by inflammation. A raised sTfR may be a useful indicator of functional iron deficiency in CF.

Absolute iron deficiency - Iron stores are depleted, as indicated by serum ferritin (low), serum iron (low), transferrin (high), transferrin saturation (low), sTfR (high), CRP (normal)

- Oral iron supplementation is recommended

Functional iron deficiency - Iron stores are normal-high but not available at the site of erythroblast production. Serum ferritin (low – normal), serum iron (low), transferrin (normal-high), transferrin saturation (low), sTfR (high), CRP (high)

- Oral iron supplementation may be required

Dietary considerations
Increasing dietary iron intake is often inadequate in the treatment of iron deficiency in CF. Iron is available in food as haem iron (more bioavailable) and non-haem iron (less bioavailable).

- Meat, seafood and poultry are good sources of haem iron.
- Plant-based foods (wholegrain cereal and green leafy vegetables) and iron-fortified foods (infant rice-cereal) are good sources non-haem iron.
- Foods high in vitamin C improve the absorption of iron.
- Foods high in calcium, phytates (legumes, rice and other grains) and tannins (tea) can inhibit the absorption of iron.

Oral iron supplement considerations
Prescribe an iron supplement, in addition to dietary change, for 2-3 months to treat diagnosed iron deficiency. Suggested treatment doses:

- Children: 3-6mg/kg/d elemental iron for 2-3 months after serum Hb normalises
- Adolescents & adults: 100-200mg elemental iron daily for 3-6 months after Hb normalises
- Gastrointestinal complaints (including constipation and epigastric pain) are common side effects of oral iron supplements.

Multivitamins are not recommended in the treatment of iron deficiency. Concerns regarding potential drug-nutrient interactions should be discussed with the CF pharmacist.

Iron supplementation is not contraindicated for people with CF with chronic Pseudomonas aeruginosa infection.

Intravenous iron supplementation

Iron (ferric carboxymaltose) 500mg/10ml injection is associated with fewer adverse events than other IV iron supplements. It is also available on the pharmaceutical benefits scheme (PBS) in Australia and via PHARMAC in New Zealand (District Health Board hospitals only).

9.2 Magnesium

Magnesium is an abundant mineral found in the body and acts as a cofactor in more than 300 enzymatic reactions, including those involved in regulation of muscle and nerve function, heart rhythm, platelet-activated thrombosis and bone formation [43,428]. Plant and animal-based foods such as green vegetables, unrefined cereals, legumes, nuts, and shellfish provide good sources of magnesium [428]. Highly processed foods such as highly refined flours, oils and fats are low in magnesium [43,428]. Hypomagnesaemia, defined as low serum magnesium, is not common but has been observed in the CF population [429-431].

Disease Aetiology

Magnesium homeostasis is primarily controlled by the kidneys [429,432]. Causes of hypomagnesaemia in the general population include [432]:

- Redistribution of magnesium – often seen in refeeding syndrome
- Reduced dietary intake of magnesium
- Gastrointestinal malabsorption
- Renal disease
- Endocrine – diabetes mellitus and hyperaldosteronism
- Drug-nutrient interactions

People with CF may be at risk of hypomagnesaemia but the mechanism for why it occurs in CF is largely unknown [429-431]. The following reasons are thought to potentially contribute to hypomagnesaemia in CF [429]:

- Frequent use of aminoglycosides that may result in long-term renal damage and tubular leak of magnesium
- CF-related diabetes with increased sodium and magnesium losses via diuresis [433]
- Malabsorption whereby magnesium binds to fat in faecal fat excretion [434]

Hypomagnesaemia has been reported in a retrospective analysis of biochemical parameters for patients referred for lung transplant, whereby 57% of patients had serum magnesium levels below the reference range for age and sex [429]. However, the true prevalence of magnesium deficiency and/or hypomagnesaemia in CF is unknown [429,430].

Assessment

DIET

Magnesium deficiency due to inadequate dietary intake is not common [432]. However, adequacy of intake should still be considered as part of a thorough nutrition assessment, especially for people with CF who have poorly controlled fat absorption or show signs/symptoms of a potential deficiency.

Foods high in magnesium are outlined in Table 9e below. These include green leafy vegetables (i.e. spinach), nuts and seeds, fish, legumes and unrefined cereals [43]. The recommended RDI of magnesium based on age and sex is outlined in Table 9f [43].

Table 9e. Magnesium containing foods (mg per serve) [435]

Foods containing Magnesium	Serving Size	Magnesium content (mg)
Animal-based sources		
Chicken	100g	28
Beef (mince)	100g	29
Salmon	100g	29

...table continued overleaf

Foods containing Magnesium	Serving Size	Magnesium content (mg)
Plant-based sources		
Almonds	30g	78
Cashews	30g	75
Peanuts	30g	48
Soy milk	1 cup	55
Peanut butter	1 Tbspn	45
Wholemeal bread	2 slices	50
Rice (brown) cooked	½ cup	44
Yoghurt	1 cup	39
Oats (raw)	¼ cup	31
Banana	1 banana	30
Potato (baked)	1 potato	26
Cow's milk	1 cup	26
Kidney beans	½ cup	28

Table 9f. Recommended Dietary Intakes of magnesium for people in Australia and NZ, mg/day [43]. *Available at: http://www.nrv.gov.au/*

Recommended Dietary Intake (RDI) for Magnesium		
Age	**Male** (mg/day)	**Female** (mg/day)
Infants		
0-6 months	30*	30*
7-12 months	75	75
Young children		
1-3 years	80	80
4-8 years	130	130
Children & adolescents		
9-13 years	240	240
14-18 years	410	360
Adults		
19-30 years	400	310
31-50 years	420	320
51-70 years	420	320
>70 years	420	320

* Adequate Intake (AI)

CLINICAL

Early clinical symptoms of magnesium deficiency may include [428]:

- Loss of appetite
- Nausea and vomiting
- Fatigue and weakness

As magnesium deficiency worsens, symptoms may include [428]:

- Numbness and tingling
- Muscle contractions and cramps
- Seizures
- Sudden changes in behavior and personality changes
- Abnormal heart rhythm and coronary spasms

Symptoms of magnesium deficiency are often not experienced until serum magnesium levels drop below 0.5mmol/L [432]. It is not uncommon for patients to present with no signs or symptoms of magnesium deficiency, even with severe hypomagnesaemia, if serum concentration declined gradually [428]. Hypomagnesaemia commonly co-exists with other micronutrient deficiencies, particularly hypokalemia and hypocalcaemia [432].

BIOCHEMICAL AND LABORATORY DATA

Serum magnesium concentration does not reflect total body magnesium levels as only 1% of total body magnesium is present in the extracellular fluids [428]. Magnesium is primarily concentrated in the bones and muscles [436,437]. Total body magnesium deficiency may therefore exist in people with normal serum magnesium levels [428].

Serum magnesium measures short-term intake variation and is most helpful in detecting rapid extracellular changes [99,428]. While not always practical, a 24-hour urinary magnesium is a better marker of body stores [428].

- High urinary excretion indicates renal wasting of magnesium
- Low urinary excretion suggests an inadequate intake or absorption of magnesium

INTERVENTION

It has been hypothesised that oral magnesium supplementation may improve respiratory musculature in the CF population. However, only one small study has investigated this hypothesis to date. While improvements in respiratory muscle strength were shown amongst the paediatric patients studied, there is currently insufficient evidence to recommend routine supplementation of magnesium above reference intake values [99].

Does supplementing magnesium above the RDI improve nutrition and/or respiratory outcomes in people with CF? PICO 9.2.1

[Grade D] There is insufficient evidence to support that routine magnesium supplementation above the RDI improves health outcomes in people with CF. Explore the use of oral magnesium supplementation only when dietary intake is unable to meet the RDI. [99]

Monitoring and Evaluation

There is no evidence to guide practice for the ongoing monitoring and evaluation of magnesium status in CF. Clinical judgment should be applied when determining if or when to review magnesium status for a person with CF.

Practice Points PICO 9.2.1

Encourage people with CF to achieve adequate consumption of magnesium as part of a varied diet.

- Foods high in magnesium include green leafy vegetables, unrefined cereals, legumes, nuts & shellfish
- Magnesium deficiency is likely to co-exist with other micronutrient deficiencies. A nutrition review should therefore consider overall micronutrient adequacy.

Oral magnesium supplementation is considered safe and cost-effective. High dose magnesium supplementation may result in gastrointestinal side effects, especially diarrhoea. This is most commonly seen in patients on higher dose magnesium supplements after lung transplantation.

9.3 Calcium

This section provides a general outline of the nutrition considerations for calcium and CF. Due to a lack of supporting literature no PICOs have been answered for this chapter. Refer to Chapter 13 for more detailed information about the relationship between calcium and bone health.

Calcium plays a crucial role in the development and maintenance of the skeleton with 99% of the body's calcium found in the form of *'hydroxyapatite'* (bone mineral) [438]. Calcium is also involved in cardiac function and neuromuscular facilitation [43]. Calcium status may be compromised in the CF population due to vitamin D deficiency or inadequate intake of dietary calcium [78].

Disease Aetiology

Parathyroid hormone (PTH) and 1,25-dihydroxycholecalciferol ($1,25(OH)_2D$) controls calcium homeostasis [438].

- PTH – increases distal tubular renal calcium resorption and bone resorption [438]
- $1,25(OH)_2D$ – increases intestinal calcium absorption [438]

Negative calcium balance enhances resorption of bone to maintain extracellular calcium homeostasis [439]. For the general population and people with CF, a negative calcium balance is known to increase the risk of low bone mineral density and fractures [149]. The pathogenesis of negative calcium balance and low bone mineral density in CF remains uncertain. It is thought to be multifactorial with potential causes including:

- Dietary - inadequate calcium intake, poor nutritional status and high protein and sodium intakes which may increase urinary calcium excretion [440]
- Infection and inflammation [149,441]
- Glucocorticoid use [149,442]
- Hormonal status [443]
- The incorporation of calcium into insoluble micelles with dietary fat [444]
- Vitamin D - increased prevalence of vitamin D deficiency in people with CF may exacerbate dietary calcium deficiency through reduced gastrointestinal absorption [445]
- Malabsorption – even with optimal pancreatic enzyme replacement (PERT) dosing, some calcium may be lost via dietary malabsorption and increased endogenous faecal losses [391,446]

The prevalence of negative calcium balance in the CF population is unknown [149]. However, it is well established that people with CF have a high prevalence of low bone mineralisation [441].

Assessment

When assessing calcium intake, bone health (Chapter 13) and vitamin D (Chapter 8) should also be considered.

DIET

Review dietary intake of calcium containing foods, see Table 9g. Foods high in calcium include dairy foods (i.e. cow's milk, cheese & yoghurt), fortified plant-based milks (i.e. soy milk), firm tofu & bony fish. Legumes, nuts and some green vegetables also contain small amounts of calcium.

Calcium intake should be assessed annually and compared to national recommendations for age and sex in the general population [391]. As seen in Table 9h, the recommended dietary intake (RDI) for calcium varies throughout different life stages [43]. Overall calcium requirements are higher during periods of rapid growth i.e. infancy and throughout the pubertal growth spurt [438].

CLINICAL

In addition to dietary calcium intake, the following should be considered when assessing calcium status in the context of CF:

- Vitamin D status – vitamin D deficiency may exacerbate dietary calcium deficiency through reduced gastrointestinal absorption [445]
- The impact of poor nutrition status and high protein and sodium intake on urinary calcium excretion [440]
- The impact of infection and inflammation on bone remodelling [149,441]

- Drug-nutrient interactions [438]
  - Proton pump inhibitors may indirectly reduce calcium salt solubility due to a reduction in gastric acid
  - Glucocorticoid use may result in poor gastrointestinal calcium absorption and increased renal calcium excretion
  - Calcium can interfere with the absorption of other medicines (particularly bisphosphonates, iron and some antibiotics e.g. ciprofloxacin)
- Pancreatic enzyme replacement therapy (PERT)
  - Poor adherence or under-dosing of PERT may result in malabsorption and increased endogenous faecal calcium losses [446]
  - Adequate PERT is required for lipolysis to prevent the excretion of calcium in soaps [78]

Potential side effects of excessive calcium supplementation, above the RDI (Table 9h) include [439]:

- Hypercalcaemia and hypercalcuria
- Nephrolithiasis
- Constipation
- Vascular and soft tissue calcification
- Interactions with zinc and iron absorption

Table 9g. Calcium containing foods (mg per serve) [435]

Calcium containing foods	Serving Size	Calcium content (mg)	mg/100 g
Dairy sources			
Milk	1 cup	304	124
Natural yogurt	200g	386	193
Cheddar cheese	1 slice	160	739
Vanilla ice cream	1 scoop	48	93
Vanilla custard	100g	130	130
Non-dairy sources			
Tofu (firm)	1 cup	832	320
Pink salmon (canned in water)	1 small can	279	310
Snapper	1 fillet	163	160
Tahini	1 Tbspn	66	330
Almonds	10 almonds	30	220
Dried figs	6 figs	160	200
Dried apricots	6 apricots	32	67
Brazil nuts	10 nuts	53	150
Bok choy	1 cup	65	83
Silverbeet	½ cup	87	72
Lebanese cucumber	1 cup	68	63
Broccoli	2 florets	15	32
Baked beans in tomato sauce	1 cup	43	39
Chickpeas (canned)	1 cup	90	45
Soy beans (canned)	1 cup	106	59
Boiled egg	1 egg	21	39
Licorice	1 stick	34	280

Table 9h. Recommended Dietary Intake of calcium for people in Australia and NZ, mg/day [43].
Available at: http://www.nrv.gov.au/

Recommended Dietary Intake (RDI) for Calcium		
	Males (mg/d)	**Females** (mg/d)
Infants		
0-6 months	210*	210*
7-12 months	270*	270*
Young children		
1-3 years	500	500
4-8 years	700	700
Children & adolescents		
9-11 years	1000	1000
12-13 years	1300	1300
14-18 years	1300	1300
Adults		
19-30 years	1000	1000
31-50 years	1000	1000
51-70 years	1000	1300
>70 years	1300	1300

* Adequate Intake (AI)

BIOCHEMICAL AND LABORATORY DATA

There are no simple biochemical measures available to assess calcium status [149,391]. It is recommended that dietary calcium intake, as assessed by a dietitian, be considered in conjunction with vitamin D status (Chapter 8) and additional bone health considerations (Chapter 13) [439,447].

Intervention

Calcium should be optimised via dietary sources where possible [149,438]. In particular, dairy products are recommended as good sources of dietary calcium [78]. If unable to meet nation specific recommendations for daily calcium intake, an oral calcium supplement is recommended, see Table 9i [78,149,438].

Points to consider with oral calcium supplementation:

- The timing of oral calcium supplements should be considered in the context of the patient's overall management goals.
- Where possible, calcium supplements should not be taken at the same time as medications with a known drug-nutrient interaction e.g. bisphosphonates, iron supplementation and some antibiotics e.g. ciprofloxacin.
- Glucocorticoids and proton pump inhibitors may inhibit the gastrointestinal absorption of calcium.

Table 9i. Readily available calcium supplements in Australia (mg per serve)

	Calcium (mg) per tablet	Vitamin D (IU) per tablet
Caltrate®	600	-
Caltrate with Vitamin D®	600	400
Ostelin Kids Vitamin D and Calcium®	350	300
Ostelin Vitamin D and Calcium®	600	500

Refer to http://www.pharmac.govt.nz/Schedule for a list of current calcium supplements available in New Zealand.

Monitoring and Evaluation

It is recommended that calcium intake be assessed annually, in conjunction with a thorough nutrition assessment whereby adequacy of energy and protein intake is also assessed [78,149,438]. More frequent review of dietary intake is recommended for people with poor height growth velocity or weight loss [78,149]. Where possible, it is also recommended that intake is assessed by a dietitian with specialist CF knowledge [149,438].

For CF patients with renal impairment, serum calcium levels should be monitored closely [438].

9.4 Sodium

All people with CF are at increased risk of sodium deficiency as a result of increased sweat losses [1,279]. Sodium plays a role in fluid balance and blood volume maintenance [43,448]. Sodium chloride, most commonly referred to as 'salt', is found naturally in some foods in small amounts. The vast majority of dietary sodium is added to food as a flavour enhancer or preservative.

Disease aetiology

The primary defect in CF, a mutation in the CF transmembrane conductance regulator (CFTR) gene, affects the function of cell chloride channels and prevents the usual flow of sodium and chloride ions and water in and out of cells. As a result, people with CF have abnormally high sodium and chloride losses via sweat glands and are at an increased risk of dehydration, hyponatraemia (low serum sodium) and hypochloridaemia (low serum chloride) [449,450]. The sodium concentration of sweat in the CF population is usually 3-5 times that of the general population [451].

Factors identified that increase the risk of sodium deficiency (hyponatraemia and dehydration) in CF include:

INFANCY

- Increased requirements due to periods of rapid growth and a large body surface area [279]. Overall infants have increased salt losses via their skin, especially in hot and humid temperatures [202].
- Lower sodium content of breastmilk (approximately 7mmol/L) compared with infant formula (up to 15mmol/L) [452,453]
- Low sodium content of many first complementary foods [78]

ILLNESS

- Reduced sodium intake associated with poor appetite [1]
- Increased losses when febrile [1]
- Increased losses via ileostomy (common in infancy post bowel surgery for meconium ileus) [1]

COMPOSITION OF ORAL AND ENTERAL NUTRITION SUPPORT SUPPLEMENTS

- Relatively low sodium composition of supplementary oral and enteral feeds [1]

SWEAT COMPOSITION AND RATE

- People with CF have been found to have higher sweat rates, particularly during exercise [454-456].
- The excretion of sweat is nearly isotonic to plasma and can diminish the thirst drive [451,455,457] .

EXERCISE

- In the healthy population, an individual's sodium sweat losses with exercise vary depending on dietary intake, sweat rate, hydration and heat acclimatisation [458]. Prolonged and strenuous physical activity, especially in the heat can result in significant sodium losses [458].
- When exercising in hot and humid conditions, CF sweat sodium losses can be 10 times that found in the non-CF population [279].
- Children with CF have been found to drink less during exercise, likely as a result of a reduced hyperosmotic trigger diminishing thirst drive [100,450].

How do environmental factors and exercise impact on sodium requirements for people with CF compared to those without CF? PICO 9.4.1

[Grade C] Climate (heat and humidity) is thought to have an impact on salt requirements in CF. There is also some evidence to support an altered thirst drive for people with CF. However, at this time, there is insufficient evidence available to conclude how environmental factors and exercise impact on sodium requirements for the wider CF population. [100-102]

The prevalence of sodium deficiency in the CF population is unknown. The literature is primarily limited to case studies, especially in infants [202].

Assessment

DIET

As part of a thorough nutrition assessment, a CF individual's sodium intake should be considered as well as their potential risk of sodium deficiency and hyponatraemia [285]. Check for the following:

- Periods of illness, due to reduced intake associated with poor appetite and increased losses if febrile
- Periods when regular dietary intake is decreased and is replaced by oral fluid supplements or enteral nutrition support, which have low sodium content
- Periods of increased exercise and/or exposure to hot/humid environments
- Intake during infancy
- Canned, processed and convenience/fast foods are generally high sodium containing foods

CLINICAL

Signs and symptoms of sodium deficiency to consider as part of a thorough nutrition assessment include: nausea and/or vomiting, muscle cramps, deposition of salt crystals on the skin, fatigue, poor growth (especially in infants), headaches, difficulty expectorating sputum, constipation, DIOS and hyponatraemia [1,411,459]. Some antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRIs), may cause increased sweating and hyponatraemia, especially on commencement.

BIOCHEMICAL AND LABORATORY DATA

Serum sodium alone is not a sensitive marker for salt depletion in CF [1]. The interpretation of biochemical markers for assessing salt depletion in people with CF should therefore be done in conjunction with a thorough clinical assessment[1]. If total body salt depletion is suspected, spot urine sodium analysis should be conducted [460]. Sodium deficiency is confirmed with urinary sodium concentrations <10 mmol/L [285].

Intervention

What is the recommended daily sodium requirement for people with CF compared to those without CF? PICO 9.4.2

[Grade D] There is a lack of research available to guide sodium requirements for people with CF. As a result, recommendations vary in international consensus and review documents. Recommendations for daily sodium requirements in CF are:

- Infants - 500-1000mg
- Children - 1000-4000mg
- Adolescents and adults - 6000mg

(unchanged from the '*2006 Australasian Clinical Practice Guidelines for Nutrition in CF*[1])

Table 9j. Recommended daily sodium requirements (mg/d) for people with CF in Australia and NZ[1] compared to the general population [43].

	Recommended Dietary Intake for Sodium mg/d (mmol/d)	
Age	**CF population**	**General population**
Infants	500-1000 (22-44)	120-170 (5-7)
Children	1000-4000 (44-174)	200-800 (9-35)
Adolescents and adults	6000 (261)	460-920 (20-40)

As shown with the broad range of sodium requirements provided for each age group in Table 9j, it is important to remember that sodium targets should be individualised. There is likely to be variability in sodium requirements within and between individuals. The recommended sodium dose to correct a confirmed deficiency is 1 to 2 mmol/kg/day with ongoing monitoring of serum sodium, electrolytes and urinary sodium until corrected [285,411].

Monitoring and Evaluation

The sodium requirement for a person with CF may change over time. It is important that adequacy of sodium intake, including supplementation, is reviewed on a regular basis. Particular times or periods in which this may be the case include:

- Seasonal variation - sodium requirements are likely to be higher during the warmer months of the year
- Changes in levels of physical activity and exercise patterns
- Change in work environments (particularly if required to work outdoors)
- Major changes to nutrient sources that may impact on dietary sodium intake e.g. reliance on enteral nutrition or oral supplements

A spot urine sodium analysis should be considered if sodium depletion is suspected or supplementation significantly changes. While not commonly used in clinical practice in Australia and New Zealand, other ways to monitor sodium status include:

- Fractional excretion of sodium (FENa) – aiming for a level 0.5-1.5% [78]
- Urinary sodium : creatinine ratio – aiming for 17-52mmol/mmol [78]

CF patients and the families of young children should also be taught to identify times when sodium requirements may be elevated, signs and symptoms of potential salt depletion and be provided with a guide to increase sodium supplementation as required. It is important to remember that level of thirst should not be relied on to estimate fluid requirements because a low serum osmolality may diminish thirst drive [100].

Practice Points PICO 9.4.1

Take into account the following when evaluating sodium requirements:

- Infants & people with CF exposed to hot / humid environments or illness are at high risk of sodium depletion & hyponatraemia.
- Signs & symptoms of sodium depletion include nausea, vomiting, muscle cramps, deposition of salt crystals on the skin, fatigue, poor growth (especially in infants) and/or hyponatraemia
- Sweat sodium losses vary amongst individuals (with and without CF)
- Dietary intake, sweat rate, hydration and heat acclimation can impact on sodium losses.

Sweat rates/sodium losses are elevated and thirst drive potentially diminished for people with CF in hot / humid conditions and during exercise. Dehydration/hyponatraemia is a risk under these conditions.

Practice Points PICO 9.4.2

- Clinicians should continue to use nation-specific guideline/consensus documents (including the '*2006 Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis*' in addition to a thorough nutrition assessment and clinical judgment as a guide when recommending sodium supplementation to people with CF [1].
- Serum sodium is not a sensitive marker for salt depletion in CF.
- Undertake a spot urine sodium analysis if sodium depletion is suspected or supplementation significantly changes.
- Clinicians should be guided by local climate-based recommendations and clinical judgment when individually tailoring sodium supplementation to people with CF.

Translating into Practice

Tips to increase sodium intake during infancy:

- Formula fed infants – divide recommended salt dose across a minimum of 3-4 formula bottles.
- Breastfed infants – a small amount of salt can be placed on a clean finger and the infant can suck the salt from the finger prior to a feed. Parents usually measure the recommended dose out at the beginning of the day and work through this with each feed.
- Pancreatic insufficient infants – salt can be added to the apple (or fruit) puree used to administer the pancreatic enzyme replacement therapy (PERT).
- Salt solution – recommended salt can be mixed with a small amount of water and administered to infants via a syringe in small doses throughout the day. This is best given prior to a feed as may cause vomiting in some infants.

Tips to increase sodium intake for children, adolescents and adults with CF:

- Add salt to food and cooking
- Encourage salty foods (see Table 9k below)
- Homemade salt capsules – fill empty gelatine capsules (available from retail pharmacy) with table salt.
- Commercial supplements (see Table 9l below)
- Homemade sports drinks – ¼ teaspoon salt (580 mg) added to 500 mL cordial solution

Useful sodium conversions

- 1 tsp salt (NaCl) = 2,300mg sodium
- 1mmol Na^+ = 23mg sodium
- 1g salt (NaCl) = 17.1mmol Na^+ = 393 mg sodium

Table 9k. Examples of foods high in salt [461]

Foods containing approximately 1/8 teaspoon salt (290mg sodium)	Foods containing approximately **¼ teaspoon salt (580mg sodium)**
50g packet salted potato or corn chips 1/3 cup salted peanuts or mixed nuts 1 cheese & crackers dip snack 2 slices of bread 1 wrap or piece of Lebanese bread 1 large croissant 1 ½ teaspoons Vegemite® 1 ½ tablespoons tomato or barbecue sauce 5 olives 3 small (2cm) cubes feta cheese 1 small can tuna (in brine, drained) 2 slices (60g) BBQ chicken, with skin 1 tablespoon capers	½ cup pretzels 2 slices processed meat (i.e. ham or salami) 1 rasher of bacon 2 slices processed cheese 1 slice haloumi cheese 1 meat pie 2/3 large sausage roll ¾ cup fried rice 6 chicken nuggets 1 ½ slices pizza ½ cup baked beans ½ serve 2 minute noodles (with flavouring) 2 teaspoons soy sauce 1 sausage (thick) 1 cheese and bacon roll

Table 9l. Commercial salt supplementation products available in Australia and New Zealand. Refer to http://www.pharmac.govt.nz/Schedule for a more detailed list of rehydration solutions available in New Zealand.

Product	Sodium (mg)	Sodium (mmol)
Commercial sports drinks		
Gatorade®per 100mL	51	2.2
Powerade®per 100mL	42	1.8
Gatorade Endurance®per 100mL	84	3.6
Staminade®per 100mL	29	1.3
Rehydration solutions		
Gastrolyte® (per 5g sachet)	278	12
Hydralyte® (per 5g sachet)	206	9
Glucolyte® (per 40g sachet)	248	10.7
Hydralyte Sports® (per 17.9g sachet)	690	30
Salt tablets		
Toppin® salt tablets (AUS)	240mg (per tablet)	10.4mmol (per tablet)
Slow Sodium 600mg tablets (NZ)	230mg (per tablet)	10mmol (per tablet)

9.5 Zinc

Zinc is essential for a number of diverse functions in the body. It plays a role in growth and development, reproduction, immune and sensory function, protein and DNA synthesis, wound healing, antioxidant protection and the stabilisation of membranes [362,462,463]. The main dietary source of zinc are animal foods as well as zinc fortified cereals [43,462].

Disease Aetiology

People most at risk of zinc deficiency:

- People with high physiological requirements – i.e. during periods of rapid growth in infancy, childhood and puberty [464]
- Pregnant and lactating women [464]
- Vegetarians due to a diet low in bioavailable zinc [463,465,466]
- Exclusively breastfed infants past 6 months of age [463,465,466]

Those with CF are also at increased risk of zinc deficiency due to pancreatic insufficiency, malabsorption and steatorrhoea. Chronic inflammation and increased oxidative stress further increases the risk of zinc deficiency in CF, as does the presence of liver disease, renal disease, diabetes, and protein energy malnutrition [463,465,466]. Treatment with pancreatic enzyme replacement therapy has been shown to improve zinc absorption [467,468].

The reported prevalence of zinc deficiency in children and adolescents with CF ranges from 0-40% [103,106,109,110,467,469]. Evidence for the prevalence of zinc deficiency in infants is limited. There have been several reports of infants presenting with signs and symptoms of severe zinc deficiency prior to the diagnosis of CF, though not all were found to be zinc deficient [467,470,471].

The clinical significance of marginal zinc deficiency is unclear. One study reports lower lung function and an increased prevalence of bone disease and impaired glycaemic status in people with CF who have sub-optimal zinc levels [108]. In contrast, no correlations between plasma zinc levels and growth, lung function and infection have been reported in other studies [103,107,109,110,472].

Zinc is generally considered to be relatively nontoxic [465]. There is no evidence of adverse effects from naturally occurring zinc in food [43,462].

Assessment

Zinc status is difficult to measure due to the absence of obvious signs and symptoms of deficiency and in the absence of a reliable biomarker or functional indicator. There is no universally accepted single measure suitable to accurately assess the zinc status of an individual [281,362]. Where zinc deficiency is suspected, diagnosis requires examination of the whole clinical picture to identify possible causes and consequences [464]. It is important to use a combination of dietary, biochemical and functional indicators such as growth (stunting or height for age) to assess those at increased risk of deficiency [466,473].

How should Zinc status be assessed for people with CF? PICO 9.5.1

[Grade D] The level of evidence to guide practice for assessing zinc status in CF is insufficient. Further research or expert consensus is required. [103]

DIET

As part of a thorough nutrition assessment consider dietary intake of foods high in bioavailable zinc such as meat, fish, poultry and fortified cereals. Phytates inhibit zinc absorption and a high intake of phytate containing foods e.g. unrefined cereals, legumes and nuts should also be considered with a dietary assessment. However, food processing, soaking and germination can reduce phytate content and increase absorption of zinc [251,466,473]. See Table 9m below for foods high in zinc. There is considerable individual variation in daily zinc intake which needs to be taken into account when assessing usual intake.

Zinc requirements for the general Australian and New Zealand population are outlined in Table 9n.

Table 9m. Zinc containing foods [474]

	Serving Size	Zinc content (mg)	mg/100 g
Milk	1 cup	0.93	0.36
Natural yogurt	200 g	1.22	0.61
Cheddar cheese	1 slice	0.25	3.61
Vanilla ice cream	1 scoop	0.15	0.23
Vanilla custard	100g	0.39	0.39
Chicken breast (no skin)	100g	6.21	6.21
Beef mince	100g	0.92	0.92
Salmon	100g	0.46	0.46
Oysters	4 oysters	3.53	14.7
Lobster	1/2 lobster	3.52	3.4
Prawns	6 prawns	2.6	1.5
Barley	1 cup	1.76	0.9
Mixed grain bread	1 slice	0.52	52
Almond	10 nuts	0.41	3.4
Brazil nuts	10 nuts	1.35	4.1
Mussels	4 mussels	1.09	3.4

Table 9n. Recommended Dietary Intake of zinc for people in Australia and NZ, mg/day [43].
Available at https://www.nrv.gov.au/nutrients/zinc

Recommended Dietary Intake (RDI*) for Zinc		
	Males (mg/d)	**Females** (mg/d)
Infants		
0-6 months	2*	2*
7-12 month	3	3
Young children		
1-3 years	3	3
4-8 years	4	4
Children & adolescents		
9-13 years	6	6
14-18 years	13	7
Adults		
19-30 years	14	8
31-50 years	14	8
51-70 years	14	8
>70 years	14	8

* Adequate Intake (AI)

Special attention should be given to those at increased risk of deficiency:

- Vegetarians consuming diets high in phytates. Requirements for zinc may be up to 50% greater for strict vegetarians with a high phytate intake [43,464-466].
- Infants exclusively breastfed from six months of age and not receiving dietary sources of high bioavailable zinc such as meat or fortified cereals.

Adequacy of intake of essential fatty acids and protein should also be considered, as deficiencies in these nutrients may manifest clinically similar to zinc deficiency.

CLINICAL

Zinc deficiency results in non-specific signs and symptoms that may include [43,251,462,464]:

- Growth retardation
- Delayed sexual maturation
- Anorexia
- Mental lethargy
- Alopecia
- Diarrhoea
- High rates of infection, skin lesions and impaired wound healing due to immune dysfunction

A number of disorders may present with signs and symptoms similar to zinc deficiency and differential diagnosis needs to be considered [473].

Medications and supplements may interfere with zinc absorption [462,463]:

- High dose iron supplements ≥60mg elemental iron impairs zinc absorption [473]
- Calcium supplementation does not impair zinc absorption [473]
- The oral contraceptive pill, oestrogen and corticosteroids may impair zinc absorption [463,464]

Zinc may also interfere with copper absorption when zinc intakes are high ≥50mg/d [473].

Both acute and chronic forms of zinc toxicity exist. Acute effects include nausea, vomiting, loss of appetite, abdominal cramps, epigastric pain, diarrhoea, light headedness and headaches[43]. Symptoms of chronic toxicity include a reduction in immune function, decreased HDL cholesterol, and low serum copper concentrations [462,463,473].

Important synergies exist between vitamin A and zinc [475] and correlations have been shown between plasma zinc and retinol in CF [106,108,110]. Zinc is important in vitamin A transport as a component of retinol binding protein (RBP) [464]. A case report has shown that zinc therapy was effective in the treatment of night blindness in a person with CF and vitamin A deficiency, suggesting that the normalisation of zinc levels may be important in maintaining vitamin A status [372,476].

BIOCHEMICAL AND LABORATORY DATA

Serum or plasma zinc is the most widely used index of zinc status though sensitivity and specificity are poor particularly as a measure of marginal zinc deficiency. Plasma zinc is only 0.1% of total body pool and its concentration is tightly regulated [464]. Levels will usually be low in severe zinc deficiency, however are likely to be normal in marginal zinc deficiency states [202,251,463,477].

Serum zinc levels are affected by the following:

- Stress, trauma, infection and inflammation which may lead to falsely low levels [43,251]
- Disease states with low albumin i.e. protein energy malnutrition may result in low zinc as 80% of zinc circulates bound to albumin [463]
- Fasting status and time of day [108,251,464]
- Individual variations due to a high biological variation in serum zinc [464]
- Retinol deficiency (refractory to retinol supplementation) [372,462]

Overall, there is no evidence of benefit for routine annual assessment of plasma zinc levels and this practice is not currently recommended in recent consensus guidelines for CF [78]. Zinc levels in red blood cells are considered by some to be a more accurate measure of zinc [362], however this test is not routinely performed and evidence of its use in CF is limited to one more recent study [103].

Intervention

What are the recommendations for zinc supplementation in people with CF? PICO 9.5.2

[Grade D] There is insufficient evidence to make recommendations for routine supplementation or supplementation for suspected zinc deficiency in CF. Until further evidence is available, it is suggested that zinc supplementation be guided by recommendations in CF consensus guidelines. As per the 2016 ESPEN-ESPGHAN-ECFS CF nutrition guidelines[78], CF people at high risk of deficiency should receive the following supplementation doses for 6 months; infants (1mg/kg/d), children (15mg/d), adults (25mg/d). [103-110]

Summary of current consensus based guidelines suggest the following in terms of zinc supplementation in CF:

- Infants under 2 years of age with persistent failure to thrive despite adequate caloric intake and PERT and/or those with severe steatorrhoea, an empiric trial of zinc supplementation of 1mg elemental zinc/kg/d in divided doses for 6 months (max 15mg/day) should be considered [78,87]
- Children at high risk of zinc deficiency should trial 15mg/day of zinc for 6 months [78]
- Adults at high risk of zinc deficiency should trial 25mg/day for 6 months [78]
- A cross sectional study in adults reported routine supplementation for low plasma zinc of 50mg zinc for 3 months without evidence of excess zinc levels or adverse effects [108]

The clinical significance of marginal zinc deficiency and improvement with zinc supplementation is unclear, however positive effects have been shown on nutritional status, pulmonary function, infection rates and inflammation in children and adolescents with CF [105-107,110].

Supplemental zinc is available in CF-specific and general multi-vitamin and mineral preparations, in some cold and flu supplements and in zinc only supplements (usually 25mg).

- The CF multivitamin VitABDECK® contains 7.5mg zinc
- Elemental zinc composition of readily available zinc supplements include: [463]
  - Zinc oxide (80% elemental zinc)
  - Zinc acetate (30% elemental zinc)
  - Zinc sulfate (23% elemental zinc)
  - Zinc gluconate (14% elemental zinc)
- Readily available zinc supplements in Australia and New Zealand are outlined in table 9o

Table 9o. Readily available zinc supplements

Supplement	Tablet/Liquid (Dose)	Elemental Zinc (mg)
Liquid Zinc	10ml	13.5
Zinc Drops	1 dose (5 drops)	5.76
Blackmores Bio Zinc	1 capsule	25.0
Zincaps	1 capsule	50.0

What is the safe upper limit for zinc supplementation in CF? PICO 9.5.3

[Ungraded] There is insufficient evidence available to make a recommendation.

The upper limits established for the healthy population applies to total zinc intake from food and supplements [43]. It has been suggested that the upper limit particularly in children aged 2-3 years, is too low and should be reviewed [462,473]. Zinc is considered relatively non-toxic with supplemental intakes <50mg/d, however chronic toxicity has been observed with intakes ranging from 150 to 450mg/d in adults [473]. The impact of chronically exceeding the upper limit of zinc intake in patients with CF requires further investigation.

Monitoring & Evaluation

There is no evidence as to how often zinc levels should be assessed and how supplementation should be monitored. Only one paediatric CF Guideline provides any guidance, recommending that zinc levels should not be measured and the adequacy of supplementation be assessed by monitoring functional changes in clinical outcomes [202].

Practice Points PICO 9.5.1

Assess zinc status and monitor empiric trials of zinc supplementation using a combination of dietary, biochemical and clinical/functional indicators.

Serum/Plasma Zinc

- Measure using the local laboratory reference ranges.
- Analyse levels in the context of dietary and clinical information. Consider;
  - Zinc is an insensitive marker of deficiency however may be helpful diagnostically in severe zinc deficiency
  - Levels are best measured when person with CF is clinically stable. Where acute phase response and inflammation is suspected, check CPR.
  - There is high individual biological variation in zinc levels
  - There is diurnal variation in zinc levels and levels may reflect recent dietary intake. Recommend where possible to measure fasting levels.

...table continued overleaf

Clinical Indicators

- Marginal zinc deficiency may be diagnosed in some patients via a positive response to zinc supplementation e.g. improved growth.
- Evaluate differential diagnoses as other conditions may present with similar signs and symptoms of zinc deficiency.

Diet

- Attention should be given to those at high risk of inadequate zinc intakes/absorption;
  - Strict vegetarian diets with high intake of phytates
  - Infants older than 6 months exclusively breastfed or consuming limited high bioavailable zinc foods such as fortified cereals or meat
  - High iron supplementation

Assess adequacy of protein and essential fatty acids because deficiency may manifest similarly to zinc deficiency.

Practice Points PICO 9.5.2 and 9.5.3

Suggested supplementation doses.

- Infants (<2yrs) with persistent failure to thrive and/or those with severe steatorrhoea:
  - Consider a trial of zinc supplementation
  - 1mg elemental zinc/kg/d in divided doses for 6 months (max 15mg/day).
- Children with suspected zinc deficiency:
  - 15mg/d for 6 months
- Adults with suspected zinc deficiency:
  - 25mg/day for 6 months
- In vitamin A deficiency refractory to Vitamin A supplementation, consider an empiric trial of zinc supplementation.
- The amount of zinc in the CF-specific multivitamin, VitABDECK®, is not adequate to correct zinc deficiency and additional zinc is likely required.
- The main dietary source of zinc are animal foods as well as zinc fortified cereals
- Where practical, zinc is best tolerated if given in divided doses

Translating into Practice

The following conversions exist for zinc:

- 1mmol zinc = 65.4mg
- 1 µg/dL = 6.54µmol/L

CHAPTER 10 PANCREATIC ENZYME REPLACEMENT THERAPY

N. van der Haak & A. Kench

Pancreatic insufficiency affects 90% of the CF population [478] and refers to the significantly impaired ability of the pancreas to secrete sufficient enzymes such as lipases, proteases and amylases needed for the normal digestion of fats, proteins and carbohydrates respectively [479]. In pancreatic insufficiency, >98% of enzyme secretory capacity is lost and manifestations of maldigestion such as steatorrhoea are evident [231].

Individuals with pancreatic insufficiency require pancreatic enzyme replacement therapy (PERT) to assist fat digestion and absorption. PERT refers to gelatin capsules filled with mini-microspheres or micro-tablets of lipase, amylase and protease, usually of porcine origin. Although amylase and protease secretion from the pancreas are also affected in pancreatic insufficiency, lipase is more rapidly denatured by other proteases in the duodenum [480] and so is contained in larger amounts in PERT preparations. Fat absorption in pancreatic insufficiency is therefore much more affected than carbohydrate and protein absorption and so PERT is dosed based on the fat content of foods.
Pancrelipase brands and preparations available in Australia and New Zealand (NZ) include:

- **Creon®** (pancrelipase) – enteric coated mini-microspheres which are similar in size to food particles
  - Creon 10 000, 25 000 and 40 000 – mini-microspheres encapsulated in a gelatin capsule
  - Creon Micro (used in infants) – mini-microspheres measured and dosed using a scoop
- **Panzytrat®** 25 000 (pancrelipase) – enteric coated micro-tablets of uniform size

The above preparations all contain a combination of porcine-derived lipases, proteases, and amylases, concentrated as pancrelipase. Refer to table 10a for more information regarding the preparations and composition of available PERT in Australia and New Zealand.

Table 10a. Composition* and availability of pancrelipase preparations available in Australia and NZ

	Creon Micro® per scoop	Creon 10 000® per capsule	Creon 25 000® per capsule	Creon 40 000® per capsule	Panzytrat® per capsule
Lipase (BP units)	5000	10 000	25 000	40 000	25 000
Amylase (BP units)	3600	8000	18 000	25 000	22 500
Protease (Ph. Eur. Units)	200	600	1000	1600	1250
Granule size (diameter mm)	0.7 - 1	0.7 - 1.6	0.7 - 1.6	0.7 - 1.6	2
Available in New Zealand**	×	✓	✓	×	✓
Available in Australia**	✓	✓	✓	✓	✓

**Measured PERT activities are generally higher than the declared activities to ensure the required minimum activity at the end of shelf life*
*** At time of publication*

Novel non-porcine PERT preparations have undergone and continue to undergo investigation for use in CF in the US [125,481]. They are a proprietary biotechnology-derived formulation of cross linked lipase, protease and amylase and are stable in an acidic pH for reliable activity in the proximal small intestine. A novel device, Relizorb®, which contains lipase that digests fat as the enteral feed passes through the cartridge, has recently become available in the US. Non-enteric coated PERT preparations are not available in Australia or NZ.

The mechanism of PERT activation is outlined in figure 10a.

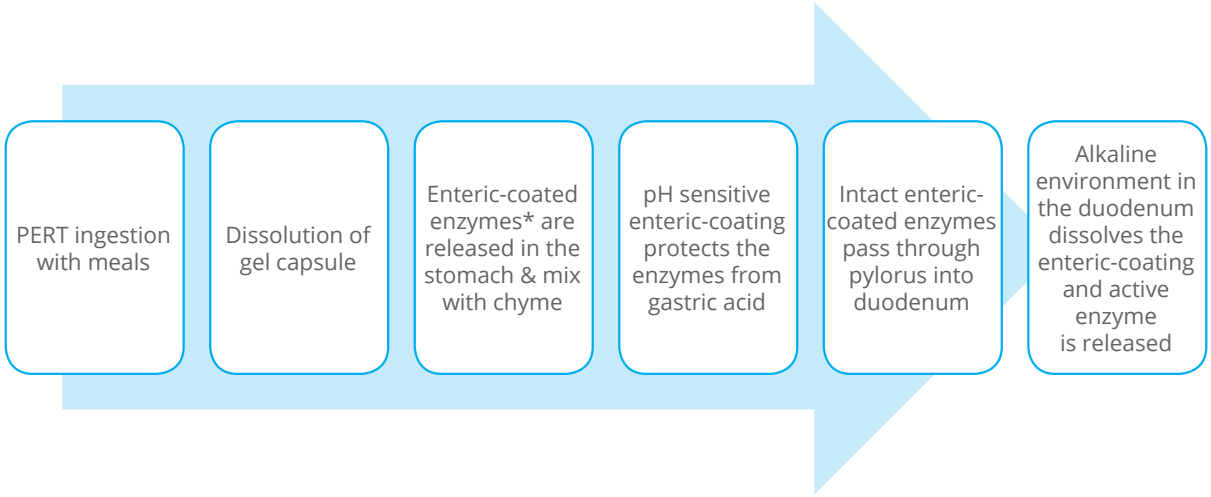

Figure 10a. Pancreatic Enzyme Replacement Therapy activation mechanism [482]

** Enteric-coated enzymes refers to the enteric coated mini-microspheres and micro-tablets*

PERT is usually administered orally with fat containing food and fluid with the aim of arriving in the duodenum simultaneously with the food or fluid. Once activated, lipase hydrolyses fats into glycerol and fatty acids ready for absorption. The ultimate goal of PERT treatment is to optimise nutrient digestion and absorption and in turn achieve optimal growth and nutritional status [483].

Disease Aetiology

PANCREATIC INSUFFICIENCY

The primary defect in CF, a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, leads to impaired chloride secretion, inhibition of bicarbonate uptake and impaired luminal bicarbonate secretion. This results in the contents of the pancreatic ducts becoming dehydrated, leading to inflammation and scarring of the acinar tissue [484]. In addition, the thick viscous secretions produced obstruct the pancreatic ducts, leading to fibrosis and impaired pancreatic enzyme secretion into the intestinal lumen. Individuals with pancreatic insufficiency require PERT to assist fat digestion and absorption.

The pancreas has a high reserve capacity and compensatory mechanisms, with clinical symptoms of insufficiency usually only manifesting when >98% of enzyme secretory capacity is lost [231]. The most severe clinical consequence of pancreatic insufficiency is steatorrhoea, characterised by fatty, frothy, offensive smelling and buoyant stools. Fat maldigestion and malabsorption can lead to fat soluble vitamin deficiencies [485], growth failure and malnutrition [486].

There are known genotype-phenotype correlations that influence pancreatic function in CF, with most individuals with a severe mutation on both alleles expressing a pancreatic insufficient phenotype [487]. Some individuals may be pancreatic sufficient at birth and develop pancreatic insufficiency in the first few years of life [488] with one study finding 21% of patients who were pancreatic sufficient at birth had developed insufficiency between 3-36 months of age [489]. These individuals are more likely to have a genotype that confers pancreatic insufficiency [490].

PANCREATIC SUFFICIENCY

A small percentage of people with CF are classified as pancreatic sufficient. These individuals usually carry a mild mutation on one or both alleles. Although these patients are deemed pancreatic sufficient, pancreatic function is not entirely normal [231]. A wide range of pancreatic function is observed in pancreatic sufficient individuals with CF, however secretory capacity is not impaired to the point that steatorrhoea becomes evident. Some individuals with pancreatic sufficiency are at risk of progressing to pancreatic insufficiency, particularly after the development of recurrent episodes of pancreatitis [232].

ACUTE PANCREATITIS

Acute pancreatitis is a known but uncommon manifestation of CF and is characterised by abdominal pain associated with inflammation and swelling of the pancreas. The presence of acinar tissue is necessary for pancreatitis to occur and it therefore rarely occurs in individuals with pancreatic insufficiency, while individuals with pancreatic sufficiency have been reported to have a 22% risk of developing pancreatitis in their lifetime [232]. Moreover, patients with

pancreatic sufficiency and CFTR genotypes associated with mild disease phenotypes have a greater risk of developing pancreatitis than patients with pancreatic sufficiency and genotypes associated with moderate to severe disease phenotypes. With sufficient tissue destruction in pancreatitis, progressive loss of pancreatic acinar tissue function can lead to insufficiency over time [491].

Assessment

Assessment to determine pancreatic insufficiency should be coordinated by or managed in conjunction with a specialist CF gastroenterologist. In centres where a specialist CF gastroenterologist is not available, advice should be sought from a major CF centre for areas of uncertainty. For people with confirmed insufficiency, assessment should focus on adequacy of PERT dosing and administration.

DIET

For people with CF and confirmed pancreatic insufficiency, the following should be considered in relation to PERT when conducting a dietary assessment:

- Dosing - amount of PERT taken with each meal and snack, focusing on fat containing foods
- Adherence - particularly at school for the paediatric CF population
- Timing of PERT in relation to food and fluids
- Physical storage of PERT

CLINICAL

Key points to consider as part of a clinical assessment when pancreatic insufficiency is suspected include:

GENOTYPE

- People with a class I-III mutation on both alleles are more likely to be pancreatic insufficient [232].
    - If confirmed pancreatic sufficient at diagnosis, people with a class I-III mutation are more likely to develop pancreatic insufficiency within the first few years of life [488,489].
- The Pancreatic Insufficiency Prevalence score is a recently developed novel and validated classification system for mutation severity that can be used to quantitatively determine the likelihood of a patient having pancreatic insufficiency [232,492].

SIGNS AND SYMPTOMS

- Poor weight gain and/or weight loss in conjunction with abdominal pain, abdominal distention, gas, frequent stooling and steatorrhoea (frothy, oily, offensive smelling and buoyant stools) may indicate pancreatic insufficiency [478]. These signs and symptoms should also be considered when assessing PERT adequacy and efficacy.
- Small intestinal confounding factors (e.g. bicarbonate deficiency, small bowel bacterial overgrowth, bile-salt deficiency and non-CF enteropathies such as coeliac disease) may present with similar signs and symptoms to pancreatic insufficiency and should also be considered.

For people with CF and confirmed pancreatic insufficiency, gastric emptying should also be considered as part of a clinical assessment.

- Fast gastric emptying can overwhelm the functional capacity of the intestine causing malabsorption and diarrhoea [493,494].
- Delayed gastric emptying can induce satiety and inhibit further intake [493].

Does gastric emptying rate impact PERT efficacy in people with CF? PICO10.1.1

[Grade C] Gastric emptying rate may impact PERT efficacy and should be considered in people with CF. [111,112]

Studies of gastric emptying in CF have found conflicting results of accelerated [495], normal [496] and delayed [497] solid or liquid gastric emptying in CF. Although the studies to date have been small and limited to the paediatric population, one study suggests that people with CF who experience fast gastric emptying may benefit from taking PERT before a meal [112], rather than during or after.

BIOCHEMICAL & LABORATORY DATA

It is recommended that all people with CF undergo formal testing to determine pancreatic status on diagnosis. Individuals who are deemed pancreatic sufficient at diagnosis who later display signs and symptoms of fat malabsorption should undergo re-testing for pancreatic insufficiency, particularly those with two gene mutations known to be associated with pancreatic insufficiency. It has been suggested that re-testing for pancreatic insufficiency occur annually for this population group [78]. There is not universal consensus on a single test to use to determine pancreatic status. It is suggested that local guidelines are used to inform which test to use to diagnose pancreatic insufficiency and to inform frequency of screening for pancreatic insufficiency in the pancreatic sufficient CF population.

Exocrine pancreatic function is notoriously difficult to assess as the pancreas and its secretions are relatively inaccessible. A number of direct and indirect tests available to diagnose pancreatic insufficiency have been described and are listed below. More detailed descriptions of these and other tests are described in the *Australasian guidelines for the management of pancreatic exocrine insufficiency* [498].

It is important to note that direct tests are rarely used in clinical practice due to their invasive nature. Indirect tests, particularly the simple faecal elastase test, are most often used in clinical practice despite their limitations, due to being more widely available and relatively non-invasive in nature.

All tests should be interpreted in conjunction with a specialist CF gastroenterologist, and should consider the wider clinical picture including class of mutation, as well as the sensitivity and specificity of tests used. In centres where a specialist CF gastroenterologist is not available, advice should be sought from a major CF centre for areas of uncertainty.

ASSESSMENT OF PANCREATIC FUNCTION

DIRECT TESTS

Direct tests to determine exocrine pancreatic function require duodenal intubation and collection of pancreatic secretions while the pancreas is stimulated with hormones such as secretin and cholecystokinin. The secretions are sampled to determine bicarbonate and enzyme outputs. This is then compared to normal values to determine level of dysfunction.

Secretin-cholecystokinin test

- Involves pancreatic stimulation with both secretin and cholecystokinin hormones, allowing for the simultaneous assessment of ductal and acinar secretory capacity and quantification of bicarbonate and enzyme outputs [499]
- Gold standard direct test of exocrine pancreatic function but impractical for routine clinical use
- Limitations include the invasive nature of the test (anaesthesia required) and cost

Endoscopic pancreatic function test

- Uses secretin only
- Shorter pancreatic secretion collection times
- Becoming an increasingly popular method to determine pancreatic function
- Use has been criticized as the test determines only ductal function and not acinar function, and shorter sampling times can overestimate pancreatic secretory capacity, leading to an incorrect diagnosis of pancreatic function [500]

INDIRECT TESTS

The most common indirect tests to determine exocrine pancreatic function are faecal or oral tests. These tests are cheaper and easier to administer and therefore are more widely used. There are also blood tests that can be used. Some of these tests can also be used to determine PERT efficacy.
Limitations of indirect tests include:

- Less sensitive and specific than direct tests
- Faecal tests detect abnormalities that occur as a result of pancreatic dysfunction rather than the dysfunction itself

The most common indirect tests are described below and summarised in table 10b.

FAECAL TESTS

Faecal Fat Balance (FFB) – 3 day faecal fat balance test

- Considered the gold standard for diagnosing and quantifying steatorrhoea [501]
- Has been used in the past to both diagnose pancreatic insufficiency and to determine adequacy of PERT
- The test involves:
  - Consumption of a high fat diet (100g fat) for 3-5 days
  - Quantification of mean daily fat intake via a weighed food intake record
  - Collection of stools (72hrs) and coefficient of fat absorption (CFA) determined
- Steatorrhea occurs when:
  - >7% of ingested fat is excreted in the stools in patients over 6 months of age [502]
  - >15% of ingested fat is excreted in the stools in patients under 6 months of age [503]
- Declined in popularity due to its limitations
  - Inconvenient for families with potential for poor adherence
  - Cumbersome and unpleasant for laboratory staff
  - Does not distinguish between pancreatic and non-pancreatic causes of fat malabsorption [504]
  - Has a low sensitivity (41.7%) for diagnosing pancreatic steatorrhoea [504]

Faecal Elastase-1 test

- Involves the enzymatic quantification of elastase in the stool
  - Faecal elastase is a pancreatic-specific protease that unlike chymotrypsin is not degraded by intestinal passage
- Highly sensitive (96%) and specific (100%) [505]
  - Faecal elastase of <100ug/g is highly predictive of pancreatic insufficiency
- Advantages
  - Only requires a single stool sample
  - Less cumbersome and unpleasant for both families and laboratory staff
  - Not affected by PERT and therefore can be useful for establishing pancreatic status in people who have already commenced PERT
- Limitation
  - False positive results can occur with non-pancreatic diarrhoea due to dilution [506]
  - Not useful for determining efficacy of PERT

Faecal chymotrypsin test

This test is no longer used to diagnose pancreatic insufficiency as the faecal elastase-1 test has been shown to have a higher sensitivity [507].

- Based on the enzymatic quantification of chymotrypsin in a small stool sample [508]

- Simple and easy to apply in clinical practice
- Limitations
    - Chymotrypsin is variably inactivated during the intestinal passage and the faecal chymotrypsin activity does not accurately reflect pancreatic secretion of the enzyme [509]
    - PERT should be ceased prior to testing as orally administered PERT can interfere with the determination of chymotrypsin in the stool

Microscopic assessment of stools for fat globules (e.g. Sudan III test)

- Involves staining a sample of stool and observing for neutral fat globules
- Less cumbersome than the faecal fat balance test
- Variability in performance and interpretation limits the overall sensitivity and reliability of the tests
- Suggested that these tests be used to screen for malabsorption. If fat globules are present, additional tests such as the FFB test may be performed [498]

Acid Steatocrit

- Determines the amount of fat in a single stool sample
- Faecal sample is homogenised and centrifuged for 15 minutes and the lipid is separated out [510]
- Lipid phase <10% of the total volumes is considered normal in people over 6 months of age
- Correlates well with the 3 day FFB test [511]

ORAL BREATH TESTS

Several substrates, most commonly ^{13}Carbon labelled, have been used to indirectly evaluate exocrine pancreatic function using a breath test [512,513].

- Involves the labelled substrate being given orally in a test meal
- Hydrolysis of ^{13}C-labelled substrate occurs in the small intestine by pancreatic lipase. The ^{13}C-labelled metabolites are then released, absorbed from the gut and metabolised in the liver. After hepatic metabolism, $^{13}CO_2$ is released in expired breath, which is captured at 15-30 minutes intervals over 6 hours.
- High sensitivity and specificity [513]
- Limitations
    - Expensive, time consuming and not widely available test
    - The test is an indicator of fat maldigestion only and is unable to differentiate between pancreatic and non-pancreatic causes

BLOOD TESTS

Serum trypsinogen test

- Measures the amount of trypsinogen in the blood
    - Trypsin is a protease secreted by the pancreas and released into the blood as the proenzyme trypsinogen
- Sensitive and non-invasive method that can be used to screen for pancreatic insufficiency in older children
- Validated in CF with levels below 20ng/ml indicative of pancreatic insufficiency in children over 7 years of age [514]
- Limitation
    - Serum trypsinogen levels fluctuate significantly in the first decade of life and so the test is not recommended to determine pancreatic insufficiency in children <7 years of age

Table 10b. Characteristics of selected indirect methods to determine pancreatic insufficiency and/or pancreatic enzyme replacement therapy adequacy

Test	Method	Strengths	Limitations	Determines pancreatic insufficiency	Determines adequacy of PERT
Faecal Fat Balance	High fat diet eaten and stools captured for 72 hours and then analysed for fat content.	'Gold standard' when performed accurately Indication of total fat absorption. High specificity (92%).	Invasive. Labour intensive. Expensive. Poor adherence. Does not distinguish between pancreatic & non pancreatic fat malabsorption. Low sensitivity for pancreatic fat malabsorption (42%).	✓	✓
Faecal Elastase	Quantification of elastase enzyme in the stool.	Only 1 stool sample needed. Not affected by dietary fat intake Can be completed on PERT. Highly sensitive (96%) and specific (100%) for pancreatic insufficiency in CF.	False positive results can occur due to diarrhoea.	✓	×
Faecal Chymotrypsin	Quantification of chymotrypsin enzyme in the stool.	Simple	Lower sensitivity than faecal elastase. High day-to-day variations. Must be off PERT.	✓	×
Acid Steatocrit	Faecal homogenate samples micro-centrifuged and steatocrit levels determined.	Lower cost than FFB Sensitive – 100% Specific – 95%	Invasive	✓	✓
Breath tests	Labelled substrate is ingested, oxidised and expired as CO_2 indicating lipase activity.	Non-invasive Simple to administer Sensitive- 89% Specific- 81% Reproducible	Expensive Gives indirect indicator of lipase activity rather than total fat absorbed.	✓	✓

Intervention

In people with CF presenting with poor growth and/or malnutrition and frequent bowel actions on diagnosis, PERT can be initiated prior to formal tests being conducted, particularly in individuals with two gene mutations known to affect pancreatic insufficiency. It is important, however, that formal testing occurs as not all poor growth is related to pancreatic insufficiency.

Current consensus guidelines recommend that people with CF take PERT before and/or during a meal [202,479].

Does the timing of PERT administration in relation to a meal impact PERT efficacy in people with CF? PICO 10.1.2

[Grade D] Limited evidence suggests PERT is equally effective when taken before or after a meal in people with CF. It also suggests that for some individuals, changing PERT timing in relation to a meal may improve PERT efficacy. A change of PERT timing can be considered for people with symptoms of fat malabsorption or poor growth once other treatment strategies such as adherence have been taken into account. [112]

One study found that PERT was equally effective in promoting normal lipase activity when taken before or after a meal. This study also showed that for some individuals, changing the timing of PERT from before to after a meal, or vice versa, improved or normalised lipase activity [112]. A trial of changing PERT timing in relation to a meal can be considered in those with symptoms of fat malabsorption or poor growth once other treatment strategies such as adherence have been considered.

How should PERT be dosed for people with CF to support optimal fat absorption? PICO 10.1.3

[Grade D] There is inconsistent and insufficient evidence to recommend specific doses of PERT required to support *optimal* fat absorption in people with CF. A wide range of doses have been shown to be effective. [113-131]

Studies looking at optimal PERT dosing in CF differ in enzyme preparation used, dose provided, treatment duration and age of patients. A wide range of doses has been shown to be safe and effective. As a result, practice is likely to vary between clinics on a national and international basis. Despite variations in practice, the following should be considered when recommending PERT dosing in people with CF:

DOSING OF PERT

Practice in Australia and New Zealand is to recommend PERT based on grams of fat consumed. This is due to:

- Improvements in the CFA with this method compared to dosing per meal [515]
- Dosing mimicking the body's physiological response to a meal [516]

Internationally, guidelines give recommendations for both dosing PERT based on units of lipase/kg/meal and units of lipase/g of fat consumed [78,87,132,202]. Dosing per meal and snack has been used due to ease of adherence with this method compared to dosing per gram of fat intake. In clinical trials, both dosing per gram of fat [114,123] and dosing per meal [113,115-117,119-121,124-126,128,129] have been shown to be effective in children and adults.

Guidelines suggest various ranges in which to dose PERT, with a maximum of 2500 IU lipase/kg/meal and 4000 IU lipase/g fat consistently suggested [78,87,132,202]. Two small prospective dose ranging studies of short duration report no improvements in CFA with doses >500 IU lipase/kg/meal [119,120]. Larger retrospective observational studies report conflicting results of no association between PERT dose and growth outcomes [130], and higher BMI percentiles in those with a higher mean PERT dose per kg per day [131].

MAXIMUM DAILY DOSE

A maximum dose of 10 000 IU lipase/kg/day was recommended [516] following observations that doses above 6000 IU lipase/kg/meal [517] and a mean of 50 000 IU lipase/kg/day were associated with fibrosing colonopathy [518]. While this maximum is still generally accepted, the median dose in the control group of the US case-control study investigating fibrosing colonopathy was 13 393 IU lipase/kg/day [518], giving rise to the idea that this maximum may be too conservative. This may be particularly pertinent to neonates and young infants who in the newborn phase may feed up to 12 times per day and therefore may exceed the recommended dose for a short time [519]. It can also be challenging to remain below the maximum suggested dose in individuals with particularly high fat diets or who are on oral or enteral nutrition support.

While there is some suggestion that the maximum of 10 000 IU lipase/kg/day may be exceeded without harm in the short term, this should be done with caution and in consultation and regular review with an experienced gastroenterologist and dietitian. Longer term studies are required to determine whether exceeding the suggested upper limit of 10 000 IU lipase/kg/day for an extended time period is safe. Other factors contributing to poor weight gain and malabsorption related to PERT efficacy such as adherence and timing of PERT in relation to a meal should be considered before increasing PERT dose (see figure 10c). Until further evidence is available, it is recommended that health professionals in Australia and NZ follow the recommendations outlined in table 10c when dosing PERT for people with CF.

Table 10c. Pancreatic enzyme replacement therapy (PERT) - recommendations

PERT Dosing Recommendations	
Infants	Breastfeeds and infant formula • Initiate at 2500-5000 IU lipase per breastfeed or formula feed • Adjust up according to weight gain and bowel symptoms • Maximum of 10 000 IU lipase/kg/day* Solids • Approximately 2000 IU lipase/g fat • Maximum 10 000 IU lipase/kg/day*
Children, Adolescents and Adults	• 500-4000 IU lipase/g dietary fat • Maximum 10 000 IU lipase/kg/day*
General recommendations	• Aim for the lowest effective dose • Use an individualised approach • Distribute PERT throughout the day according to fat content of food and fluid consumed • Monitor weight, growth and bowel symptoms • Individuals should be encouraged to discuss PERT with clinic staff before increasing dose • Branded PERT preparations should be used Distribution • Ensure PERT is correctly distributed over the day's meals based on the fat content of food and drinks consumed Administration • Capsules should be swallowed whole or the granules mixed in with an acidic fruit puree – e.g. apple puree. NB: for infants <6 months of age this is not consistent with recommendations for the introduction of solids, however is appropriate in CF • Granules should not be chewed • PERT should be given with all meals, snacks and food containing fat • PERT may be given before, during or after a meal Physical Storage • Store capsules in an airtight container in a cool, dry place. In warmer climates it may be necessary to store the product in the refrigerator to maintain storage below 25°C – see specific product information for more information on storage • Ensure capsules have not exceeded the expiry date

Adapted from international recommendations: Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis [87] Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review [132], ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis[375] and the Australasian Clinical Practice Guidelines for Nutrition in CF [1] .

* In some situations the upper limit may need to be exceeded in the short term, such as infants feeding frequently – this should be done with caution and with regular review by a gastroenterologist and dietitian.

ENTERAL FEEDING

There is little evidence to support how PERT is best administered and optimised in people with CF receiving enteral nutrition. In the absence of sufficient evidence, a number of techniques have been described [479,520,521] including:

- Oral administration
- PERT suspended in juice
- PERT dissolved in bicarbonate and administered via an enteral feeding tube
- Administration of crushed microspheres via an enteral feeding tube

A variety of dosing options for administration of PERT during continuous feeds have also been described [483] including:

- Administration of the entire dose of PERT before a feed
- Administration of multiple doses every 3 hours during a feed

It has been suggested that enzyme activity in the gut is negligible after two to three hours and it may be appropriate to administer a lipase dose which matches the amount of fat to be delivered over three hours of continuous feeding [522]. Until further evidence is available, the following options are suggested for dosing PERT with enteral feeds:

ORAL ADMINISTRATION OF PERT

Where possible, PERT should be taken orally with enteral feeds. See figure 10b for possible options for PERT dosing with enteral feeds.

ENTERAL ADMINISTRATION OF PERT

There are situations where oral administration of PERT with enteral feeds may not be possible such as in neonates without the ability to swallow. There is insufficient evidence to provide specific recommendations for administration of PERT via an enteral feeding tube. It is important that an interdisciplinary and individualised approach including a dietitian and, where relevant, advice from experienced professionals such a gastroenterologist, neonatologist, respiratory physician and pharmacist is used when determining the method of PERT administration via a feeding tube. In centres where experienced professionals are not available, advice should be sought from a major CF centre for areas of uncertainty. Things to consider when determining the method of administration when oral administration is not possible include:

- Size of feeding tube – smaller feeding tubes may become blocked more easily
- Dissolution rate of enzymes when administered in bicarbonate – this may vary across PERT products and doses [523]
- Risk of metabolic alkalosis with bicarbonate administration
- Efficacy of PERT when crushed – enzymes may not be as efficacious when crushed and added to feed

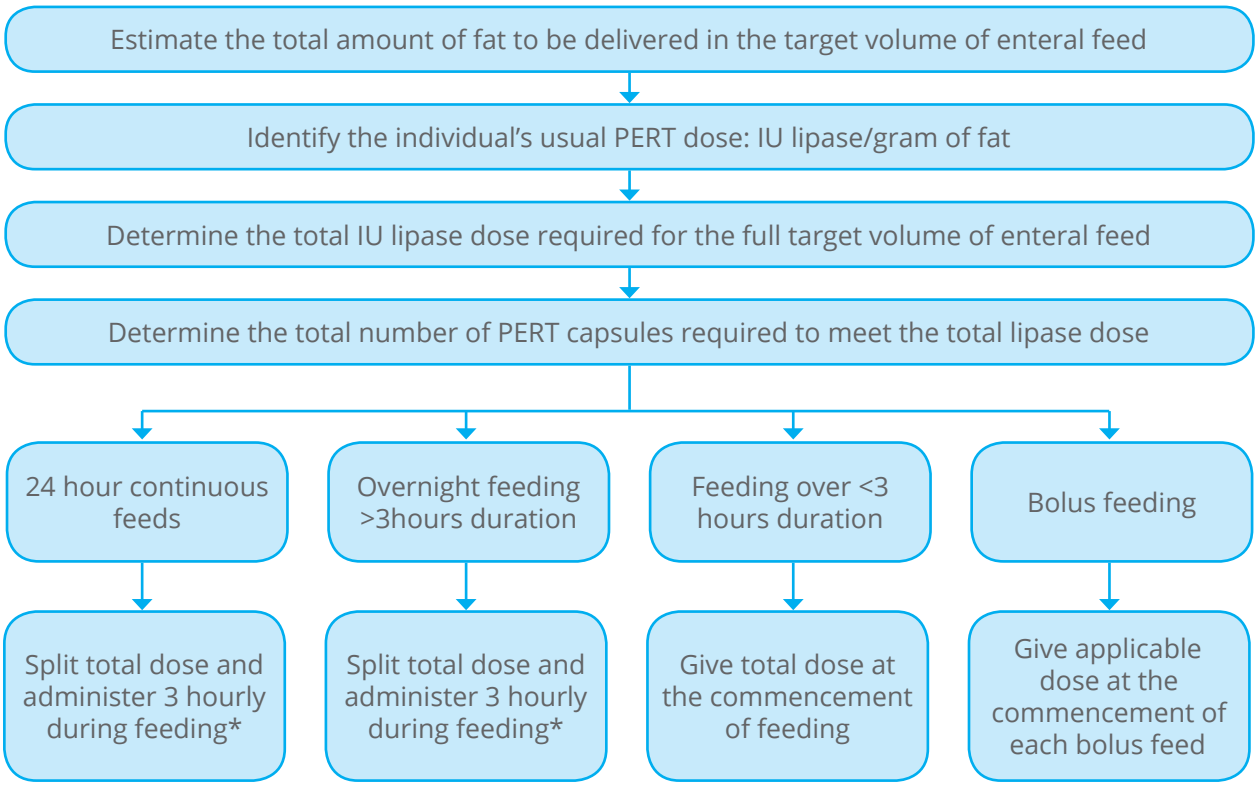

Figure 10b. Suggested dosing options for oral administration of pancreatic enzyme replacement therapy (PERT) with enteral feeds.

**In those who do not voluntarily wake or do not wish to wake overnight it may be more practical to give 50% of PERT dose at the commencement of feeding and 50% at the end.*

Additional considerations when determining administration of PERT with enteral feeds:

- **Sleeping patterns** – in patients who take PERT orally and do not voluntarily wake or do not wish to wake overnight, it may be more practical to determine total PERT dose required and give 50% of PERT dose at the commencement of feeding and 50% at the end of feeding.
- **Type of feed** – while there is little evidence as to the efficacy of elemental or semi-elemental feeds over polymeric feeds in CF, it is thought that semi-elemental and elemental feeds may be more easily absorbed without PERT due to the high proportion of total fat as MCT, however, for many patients, sufficient energy and nutrient intakes cannot be achieved with the use of elemental or semi- elemental feeds, due to their lower energy density.
    - An individualised approach should be employed when determining PERT use with elemental or semi-elemental feeds.
    - Clinical symptoms and weight gain should be monitored when determining need for PERT and dose required.
- **Family and patient preference** – it is important to work in partnership with patients and their families to develop an enteral feeding and PERT regimen that fits in with the patient's nutritional needs as well as their lifestyle.

ADJUNCT THERAPY

In people with CF and pancreatic insufficiency, the pancreas has an impaired ability to secrete bicarbonate, which can result in duodenal hyperacidity and impaired acid neutralisation [524,525]. This can lead to significantly longer periods where duodenal pH is below 4.0 in the post prandial period [526]. Most PERT preparations show 90% or greater dissolution rate within 30 minutes at a pH greater than 5.8 [527]. The lower duodenal pH in CF may therefore impair the release of enteric coated PERT, reducing their efficacy. In theory, acid suppression medication as an adjunct therapy to PERT may increase the pH of the duodenum, aiding acid neutralization and subsequently assisting PERT function therefore improving fat digestion and absorption. Early studies exploring this theory showed promising results when high doses of PERT were consumed [528].

Is there evidence to support the use of acid suppression medications to improve PERT efficacy for people with CF? PICO 10.1.4

[Grade C] There is inconsistent and limited evidence to support for or against the use of acid suppression medication to improve PERT efficacy by increasing fat absorption for people with CF. Further research is required. [133-135]

A Cochrane review investigating drug therapies for reducing gastric acidity concluded that trials have shown limited evidence that agents that reduce gastric acidity improve fat absorption [135]. Additional studies looking at acid suppression medications and PERT efficacy in CF have shown:

- Faecal fat loss decreased significantly in CF children on high dose PERT (>10 000 IU lipase/kg/d) with residual steatorrhoea after 10-20mg daily omeprazole for one month [133].
- Ranitidine as adjuvant therapy to pancrelipase in children with CF, and ranitidine and omeprazole as adjuvant therapy to pancrelipase in adults with CF, had no benefit on fat absorption [134].

ACUTE PANCREATITIS AND PERT

There is limited information specific to CF on PERT dosing in acute pancreatitis. For information on PERT dosing in acute pancreatitis in general, refer to the *Australasian guidelines for the management of pancreatic exocrine insufficiency* [498].

Monitoring & Evaluation

Efficacy and safety of PERT

All studies included in this review concluded that PERT is safe and efficacious at doses in line with current guidelines [78,132]:

- <2500 IU lipase/kg/meal OR <4000 IU lipase/g of fat
- <10 000 IU lipase/kg/day

Safety was assessed by adverse event occurrence and efficacy assessed by improvements in weight or CFA. Most studies were generally short in duration with treatment periods ranging from 3-28 days [115,118-124,127-129,529], while other studies were up to 3 months [116], 12 months [125,126] or 2 years [113].

Both Panzytrat® and Creon® have been deemed safe by the TGA (www.tga.gov.au). It is recommended that branded PERT preparations are used to ensure efficacy [132] (see table 10a).

GENETIC MODULATOR TREATMENTS

A recent study in children 2-5 years of age showed significant improvements in faecal elastase concentration after treatment with Ivacaftor, with some subjects converting from abnormal to normal faecal elastase concentrations after 24 weeks of treatment [530]. A small case report has also shown that Ivacaftor treatment has normalised faecal fat excretion and in some individuals, PERT therapy can be withdrawn [531]. It is not yet known if the same observations will be made with other genetic modulator treatments. PERT requirements for patients on Ivacaftor or other genetic potentiator and genetic modulator treatments should be assessed on an individual basis by an experienced CF team. Further information regarding genetic modulator therapy is available in **Chapter 14**.

PHTHALATES

What are the risks and long-term health implications associated with phthalate exposure via PERT to people with CF? PICO 10.1.5

[Ungraded] There is insufficient evidence to make a CF-specific recommendation.

Phthalates are a family of chemicals commonly found in everyday objects, including construction materials, furnishings, plastics, pharmaceuticals, solvents and cosmetics [532] and are generally classified according to their molecular weight. Most research into the safety of long-term exposure to phthalates has been conducted in animal studies. Small human epidemiological studies, however, have found a weak association between phthalate exposure and poor fertility, miscarriage, pre-term births and low birth weight infants [533]. Prenatal phthalate exposure has also been found to impact male reproductive development [534,535].

Some commonly used CF medications, including Creon®, contain phthalates in their enteric coating to help withstand the acidic environment of the stomach [536]. A 2009 Canadian study found measurable levels of phthalate compounds in the urine of CF children on PERT containing the low molecular weight phthalates diethyl phthalate and dibutyl phthalate [537]. Since then, all Creon® products in Australia and NZ no longer list dibutyl phthalate as an inactive ingredient. Instead, they now contain hypromellose phthalate, a high molecular weight polymer that does not convert to potentially harmful monoesters [538]. The risk of phthalate polymer toxicity is considered to be low or not known [539]. In Australia the TGA lists phthalate polymers as an ingredient for use in prescription medications without any restriction (www.tga.gov.au) and both Panzytrat® and Creon® are approved by the TGA. Exposure to phthalates via PERT should therefore not be of concern to the CF population.

Panzytrat 25 000® does not contain phthalates or the HMP polymer.

MONITORING OF PERT

PERT use should be monitored and reviewed regularly by the dietitian and interdisciplinary team in people with CF; at every clinic visit for infants, every 3 months for older children and adolescents, and every 6 months for adults [78]. Reviews should include ongoing education and support for people with CF that promotes PERT adherence. Self-management should gradually be introduced throughout the paediatric years, especially leading into and throughout adolescence.

If the response to a prescribed PERT dose is inadequate, adherence should first be addressed. This includes a review of PERT dose to ensure appropriate distribution of PERT to fat content. If adherence is considered adequate and PERT is appropriately distributed according to fat content, the following should also be considered (as outlined in figure 10c):

- Quantification of steatorrhoea
- Timing of PERT – a trial of changing the timing of PERT around the meal may be beneficial, particularly in those with suspected altered gastric emptying
- Methods used for PERT storage
- Referral to a gastroenterologist to consider and investigate potential gastrointestinal complications including role of gastric emptying rate (± formal gastric emptying assessment)

Once these factors have been considered and addressed, PERT doses can be increased over time to a maximum of 10 000 IU lipase/kg/day. PERT doses should not be indiscriminately escalated without establishing a clear rationale and a plan for evaluating the impact of the alteration in doses. This is particularly important given reports suggest a higher PERT dose is not associated with a reduction in gastrointestinal symptoms such as gas, constipation and stomach ache or reduction in number of stools [130].

Despite a lack of conclusive evidence, a trial of a proton pump inhibitor may be initiated once all other strategies to improve adequacy have been exhausted. It is important that use of a protein pump inhibitor is monitored, given mounting evidence that proton pump inhibitors are associated with significant side effects including an increased risk of fracture, hypomagnesemia and lower serum iron levels in the non-CF population [540], and may be associated with a trend toward earlier and more frequent pulmonary exacerbations in the CF population [139].

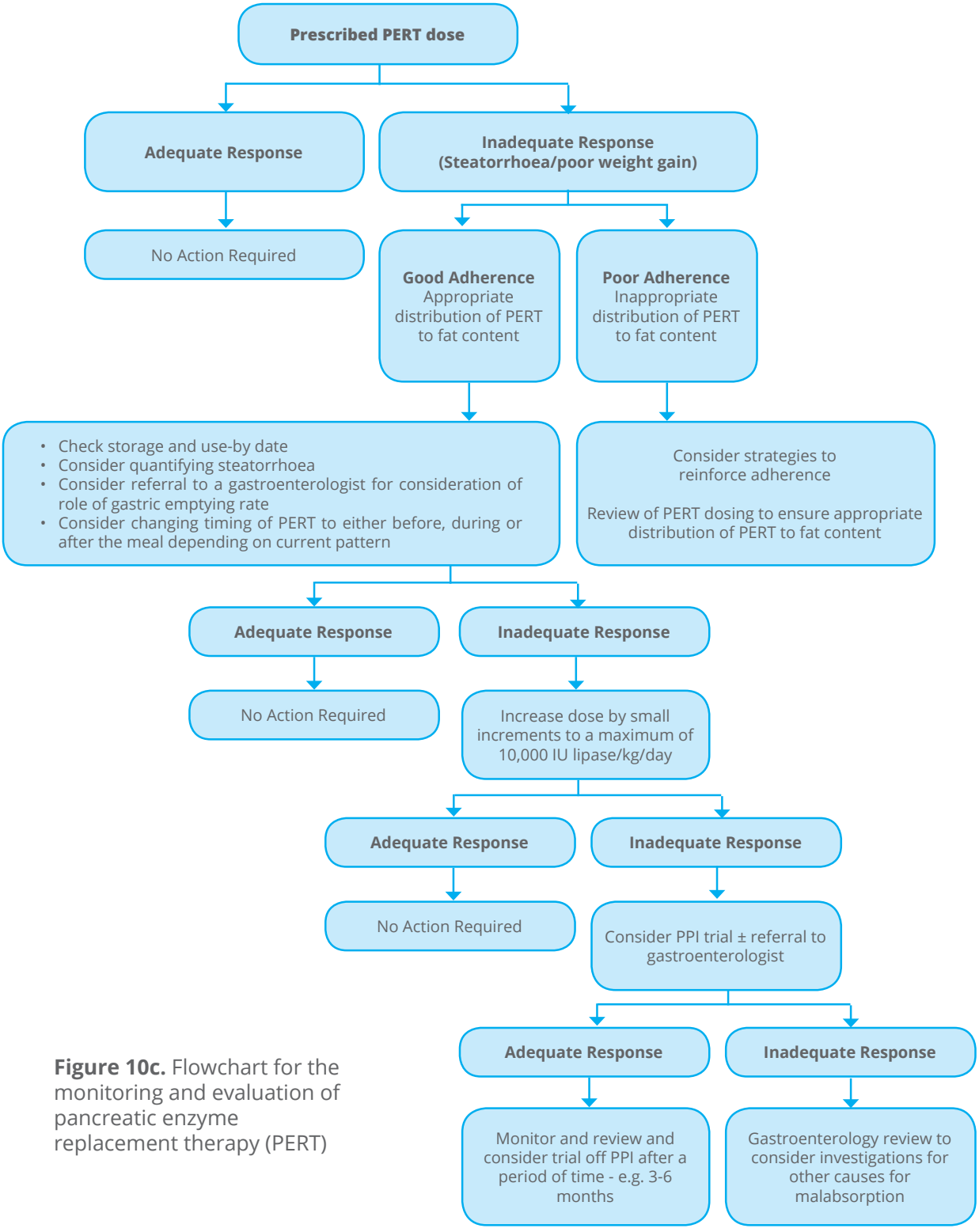

Figure 10c. Flowchart for the monitoring and evaluation of pancreatic enzyme replacement therapy (PERT)

Practice Points PICO 10.1.1 and 10.2.2

Prior to changing the timing of PERT in patients with symptoms of fat malabsorption and poor growth evaluate:

- Is the patient compliant with PERT?
- Is PERT distributed appropriately according to fat content?

Explore the role of gastric emptying rate and referral to a gastroenterologist for consideration (± formal gastric emptying assessment). People with fast gastric emptying may benefit from taking PERT before a meal.

Practice Points PICO 10.1.3

PERT Dosing Recommendations

Dosing recommendations adapted from international recommendations:

- *2006 Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis*[1]
- *2008 Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency*[132]
- *2009 Cystic Fibrosis Foundation evidence-based guidelines for the management of infants with cystic fibrosis*[87].
- *2016 ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis*[78]

Infants

- Breastfeeds and Infant Formula
  - Initiate at 2500-5000 IU lipase per breastfeed or formula feed and adjust up according to weight gain and bowel symptoms to a maximum of 10 000 IU lipase/kg/day*
- Solids
  - Approximately 2000 IU lipase/g fat
  - Maximum 10 000 IU lipase/kg/day*

Children and Adults

- 500-4000 IU lipase/g fat.
- Maximum 10 000 IU lipase/kg/day*

General PERT recommendations

- Aim for the lowest effective dose
- Use an individualised approach
- Distribute the enzymes throughout the day according to the fat content of food and drinks consumed
- Monitor weight, growth and bowel symptoms
- Individuals should be encouraged to discuss PERT with clinic staff before increasing dose
- Branded PERT preparations should be used

Distribution

Ensure PERT is correctly distributed over the day's meals based on the fat content of food and drinks consumed

Administration

- Capsules should be swallowed whole or the granules mixed in with an acidic fruit puree – e.g. apple puree. Granules should not be chewed
- PERT should be given with all meals, snacks and food containing fat
- PERT may be given before, during or after a meal**

Physical Storage

Store capsules in an airtight container in a cool, dry place – see specific product information for more information on storage. Ensure capsules have not exceeded the expiry date

* In some situations the upper limit may need to be exceeded in the short term, such as infants feeding frequently – this should be done with caution and with regular review by a gastroenterologist and dietitian

**new recommendation

Practice Points PICO 10.1.4

Take into account the following prior to commencing acid suppression medication in people with CF with symptoms of steatorrhoea and on high dose PERT:

- Is the patient adherent with PERT?
- Is PERT distributed appropriately according to fat content?
- Role of gastric emptying rate and referral to a gastroenterologist for consideration (± formal gastric emptying assessment)
- Increasing the dose by stepwise increments to a maximum of 10 000 IU lipase/kg/day
- If a trial of acid suppression medication is commenced review its effect regularly, e.g. 3-6 monthly

Practice Points PICO 10.1.5

Provide people with CF and their families with the latest information regarding phthalates and PERT on request.

Phthalate polymers, including hypromellose phthalate (HMP), are non-active ingredients in the enteric coating of many medications, including all Creon® products available in Australia and NZ.

- Unlike other phthalates that degrade to potentially harmful monoesters, phthalate polymers are considered to be of low or no known toxicity risk.
- In Australia the Therapeutic Goods Administration (TGA) lists phthalate polymers as an ingredient for use in prescription medications without any restriction (www.tga.gov.au).

All PERT products in Australia are approved by the TGA for use, therefore concern about phthalates is not an indication on its own for changing the choice of PERT preparation. Exploring such a change for an individual should be based on factors such as adequacy of control of malabsorption, and/or the occurrence of side effects.

Panzytrat 25 000® does not contain phthalates or the HMP polymer.

Translating into Practice

Determining PI

Local guidelines should be used when determining which test to use to assess pancreatic status.

Assessing PERT adequacy

Local guidelines should be used when determining how to assess PERT adequacy. The FFB test is considered the gold standard, however it is not commonly used in practice due to its cumbersome nature. It may be more practical to consider symptoms such as poor weight gain and/or weight loss in conjunction with abdominal pain, abdominal distention, gas, frequent stooling and steatorrhoea when assessing PERT adequacy.

General Tips

- A 3 day food and enzyme diary may assist in assessing PERT dose adequacy
- Providing a capsule container may assist transport of PERT and improve adherence
- PERT is reported to be effective for 30 minutes after consumption
  - For slow eaters/feeders or meals/feeds extended over a longer duration the total dose required may be split and half given at the commencement of a meal and half during or towards the end.
- PERT may be dosed per meal and snack for those who are unable to or choose not to fat count
  - Maximum of 2500 IU lipase/kg/meal has been recommended with half of meal dose given for snacks
- Requirements for PERT can change over time
- An individualized PERT plan should be discussed with the CF dietitian taking into account different environments e.g. school, university, socialising, eating out, workplace etc.
- Monitor for unnecessary increases in PERT dose
- Monitor for out of date enzymes and incorrect storage (such as in a hot car) when symptoms of malabsorption and/or poor growth are reported

...table continued overleaf

Neonates

Discuss initiation of PERT with the neonatal team if titrating from total parenteral nutrition (TPN) onto oral and/or enteral feeds. PERT is often commenced when enteral or oral feeds are at 50% of the target volume.

Infants

Available preparations:

- Australia - Creon micro® is the only PERT preparation acceptable for use
- NZ - Creon micro® is not available. Creon 10 000® is used as an alternative

Administration:

1. Place PERT granules in a small amount of acidic puree (e.g. apple puree) on the tip of a soft baby spoon
2. Place spoon under the top gum and scrape upwards, leaving the PERT and apple puree in the mouth
3. If the infant spits the mixture out, scrape it up with the spoon and repeat the above process
4. At completion of a feed, check the infant's gums for any remaining granules and remove with a clean finger as the PERT may cause mouth ulcers

Timing:

- Administer PERT immediately prior to the feed
- If feeds take >30minutes, a split dose (e.g. half at the beginning and half in the middle or end of the feed) may be required
- For infants feeding frequently, the lowest and most effective dose should be used, given frequent feeds are likely to be small in volume
- Introduction of solids:
    - PERT may not be needed with solids until greater than a tablespoon of fat containing food is consumed

Children

- Children should be switched from PERT granule preparations to PERT capsule preparations when they can swallow medications
- Tips to improve adherence:
    - PERT can be taped to foods in school lunchbox
    - The amount of PERT required with each meal and snack can be written down and provided to care-givers and teachers and/or placed in the child's lunchbox

Adolescents

- Adherence to therapies, including PERT can be challenging
    - Changing to a higher dose preparation e.g. Creon 25 000® may reduce pill burden and increase adherence, but alert to unnecessary increased in PERT dose
- Dietary intake patterns and behaviours may change (e.g. increased consumption of takeaway foods)
    - More regular review of PERT dosing may be required
    - Re-education of PERT dosing strategies including label reading may be beneficial
- Increased autonomy with PERT administration is encouraged
    - Be aware that PERT doses may be increased unnecessarily
    - An upper meal and snack dose limit guide may be beneficial for this population group

Adults

- Accuracy in identifying the fat content of meals and snacks may vary widely within and between days
    - More regular review of PERT dosing may be required
    - Re-education of PERT dosing strategies including label reading may be beneficial
- Review for unnecessary increases in PERT doses, especially in adults with persistent gastrointestinal complaints
    - Adults may increase doses of PERT to manage gastrointestinal symptoms.
    - Additional causes for GI symptoms should be reviewed to prevent unnecessary increases in PERT

CHAPTER 11 GASTROINTESTINAL & HEPATOBILIARY CONSIDERATIONS

A. Kench, J. Stonestreet, C. Painter, L. Guest, A. Matson, J. Anderson & K.Ooi

Gastrointestinal and hepatobiliary complications are important manifestations in people with CF. This chapter covers reflux, distal intestinal obstruction syndrome, constipation, screening for colon cancer and CF-related liver disease.

11.1 Gastro-oesophageal Reflux

Gastro-oesophageal reflux (herewith referred to as reflux) refers to the abnormal passage of gastric contents into the oesophagus [541]. Reflux in CF can present as either symptomatic or asymptomatic [542]. It has the potential to limit dietary intake and is therefore a risk factor for malnutrition [543,544]. Reflux may impact quality of life and potentially impact lung disease severity by increasing the risk of aspiration and reflex bronchospasm [545,546].

Disease Aetiology

It has been suggested that the primary mechanism behind reflux in CF is the inappropriate transient relaxation of the lower oesophageal sphincter [547,548]. Other potential contributing factors, specific to people with CF include:

- Increased gastro-oesophageal pressure gradient due to lower inspiratory intra-thoracic pressure [547]
- Delayed gastric emptying [548,549]
- Chronic cough [548]
- Primary pulmonary disorders caused by the accumulation of intraluminal secretions and/or destruction of airway wall and bronchiolitis [548,550]
- Medications including beta-agonists, alpha-blockers, aminophyllines, anticholinergics and benzodiazepines [551]
- Postural drainage [542,550]
- Post-transplantation complications such as vagal nerve damage, rejection or bronchiolitis obliterans syndrome [542,548,552]

Reflux is common in children and adults with CF, particularly post lung transplantation. Prevalence has been reported to range between 20 and 100 percent [548,550,553].

Assessment

Reflux may impact dietary intake through decreased appetite and tolerance of food, oral nutritional supplements and/or enteral feeds [543,544]. This in turn, may indirectly impact the individual's ability to meet their nutritional requirements.

DIET

Nutrition assessment should target volume, and frequency of meals and snacks, and if the individual receives enteral feed, the bed head elevation, feed volumes and rates of feeding.

CLINICAL

Signs and symptoms of reflux in CF include:

- Presence of heartburn, dyspepsia, acidic taste in the mouth or cough, chest pain, anorexia, nausea, vomiting, dysphagia, belching, frequent stomach gurgling, flatulence, early satiety, halitosis, pressure or a lump in the throat, hoarseness or bloating [138]
- Food refusal, failure to thrive, frequent spitting up or vomiting and colic in younger children [554]

Other considerations:

- Nutrition status, weight and weight history
- Pulmonary function history (FEV_1, FVC), and exacerbation frequency

BIOCHEMICAL AND LABORATORY DATA

Invasive investigations are not always required for the assessment and diagnosis of reflux, but may include the following:

- 24-hour pH monitoring
- 24-hour combined Multiple Intraluminal Impedance (MII) and pH monitoring
- Oesophageal manometry
- Endoscopy and biopsies
- Barium swallow

Intervention

What are the nutrition considerations for the management of gastro-oesophageal reflux (GOR) in CF?
PICO 11.1.1

[Grade D] Specific dietary factors that influence the occurrence, severity and management of GOR in CF have not been identified. Further research into the impact of dietary factors on reflux in CF is warranted. [136-139]

The following dietary and lifestyle factors may help to reduce reflux symptoms in some people with CF, although the evidence is limited:

- Performing physiotherapy treatments before meals or large snacks and in a more upright position [548]
- Eating smaller volumes of food at regular intervals may be better tolerated
- Elevating the head during overnight enteral feeding
    - Supine positioning may exacerbate reflux, and so overnight enteral feeding may result in formula being regurgitated and aspirated into the lungs [1]
    - The elevation of the head of the bed during overnight feeding in a cross-over RCT of 15 people with reflux (non-CF) demonstrated a decreased time that oesophageal pH was <4 compared with a supine position (15 and 21 percent, respectively; p <0.05) altering feed volumes and rate of feeding [555]
- If overweight, aiming for gradual weight loss
    - Studies in the non-CF population demonstrate controlled weight loss in patients with a BMI > 25 kg/m^2 improves reflux symptoms and oesophageal pH [556]
    - Avoiding high-fat meals within 2-3 hours of reclining to improve nocturnal gastric acidity[556]
- Avoiding tight clothes [557]
- Modification of postural drainage physiotherapy techniques [557]

There have been no studies performed on the cessation of chocolate, caffeine, spicy foods, citrus and carbonated beverages and their impact on reflux symptoms. Individual elimination may be considered if patients identify an association with reflux symptoms and improvement when eliminated from the diet [556].

PHARMACOLOGICAL AND MEDICAL MANAGEMENT

Histamine receptor antagonists (H_2 antagonists) and protein pump inhibitors (PPIs) for acid suppression are often first choice for reflux treatment in CF. Surgical treatment of reflux in people with CF may be considered if symptoms have not been controlled by pharmacological, dietary or lifestyle interventions. In people with CF with worsening lung function and uncontrolled reflux, some studies have shown that a Nissen fundoplication may slow the decline in lung function, decrease the number exacerbations and lead to improvements in weight. [136] The impact on pulmonary function decline remains controversial. It is important for the team to consider the potential risks and benefits of the surgery for each individual. There is an absence of long-term studies in CF, and those in the general population suggest 10% of fundoplication surgeries experience recurrent reflux symptoms [558]. Nissen fundoplication is the most common treatment for the management of reflux in the post lung transplant group [548]. Chapter 16 provides further information on the management of reflux in the context of lung transplant

Monitoring & Evaluation

No current consensus guidelines suggest formal screening for reflux disease. It is important to monitor for reflux symptoms and severity, and clinical and nutritional status as part of routine care, at all stages of the CF individual's lifespan. This should ideally occur as part of a interdisciplinary team.

The Mayo GER questionnaire (GERQ) and the Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS) are both validated self-administered questionnaires that have been used to record reflux symptoms and severity in the general population, and may be a useful tool in CF [138].

Practice Points PICO 11.1.1

- GOR is common in children and adults with CF and can present as either symptomatic or asymptomatic.
- The Mayo GER questionnaire (GERQ) and the Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS) are both validated self-administered questionnaires that have been used to record reflux symptoms and severity in the general population.
- There are no established guidelines for the diagnosis and treatments of GOR specific to CF. Use clinical judgment when applying GOR guidelines for general population to individuals with CF.
- Pharmacological therapy options to reduce the symptoms of GOR are often first choice of treatment. These include histamine receptor antagonists (H_2 antagonists) and protein pump inhibitors (PPIs).
- If dietary interventions are considered, take an individualised approach whereby nutritional adequacy is not compromised or unnecessarily restricted.
- Supine positioning may exacerbate GOR. Review bed head elevation, feed volumes and rate of feeding to optimise tolerance and reduce the risk of symptoms. Assess reflux symptoms prior to enteral feeding.
- Surgical intervention (fundoplication) may be explored if symptoms have not been controlled by pharmacological, dietary or lifestyle interventions. It is important for the interdisciplinary team to evaluate the potential risks and benefits of the surgery for each individual.

11.2 Distal Intestinal Obstruction Syndrome and Constipation

Distal intestinal obstruction syndrome (DIOS) and constipation are separate conditions, with DIOS having the potential for more severe acute implications including surgical intervention. DIOS, previously known as meconium ileus equivalent, is a known gastrointestinal complication in CF. The definitions of DIOS and constipation, according to the ESPGHAN guidelines are outlined in table 11a [559]. DIOS is characterised by a complete or incomplete intestinal obstruction with faecal accumulation in the terminal ileum and proximal colon [560]. Complete DIOS usually presents as bilious vomiting and/or fluid levels in the small intestine, abdominal pain and distension, and a faecal mass in the ileo-caecum [559,560]. Incomplete DIOS only differs by the absence of bilious vomiting on presentation [560].

Unlike the often acute presentation of DIOS, constipation usually presents with a more gradual onset of symptoms and is easily relieved with the use of aperients [559].

Table 11a. ESPGHAN CF Working Group definition for DIOS and constipation in Cystic Fibrosis [559]

Condition	Physical definition	Symptoms
Complete DIOS	Faecal mass (ileo-caecum) Complete obstruction	Bilious vomiting +/- fluid levels in small intestine plus abdominal pain +/- distension
Incomplete DIOS	Faecal mass (ileo-caecum) Incomplete obstruction	Abdominal pain +/- distension
Constipation	No intestinal obstruction	Abdominal pain +/- distension. Less frequent bowel motions +/- increased stool consistency over a period of weeks to months. Symptoms relieved after commencing laxatives

Disease aetiology

DISTAL INTESTINAL OBSTRUCTION SYNDROME

DIOS is associated with more severe CF genotypes and pancreatic insufficiency, with 34-54% of all presentations occurring in homozygous F508del patients. Conversely, DIOS is rarely seen in pancreatic sufficient patients [141,559].

Considerations for the pathophysiology of DIOS include:

- Dehydrated and thick secretions in the intestine predisposing a person with CF to obstruction [560]
- Impaired cystic fibrosis transmembrane conductance regulator (CFTR) resulting in defective water and chloride secretion into the intestine [560]
- Transluminal intestinal inflammation is thought to contribute to intestinal dysmotility and delayed intestinal transit time in CF [561]. As a result, intestinal inflammation is thought to indirectly contribute to the risk of DIOS in CF [561]

Additional factors which may increase the risk of DIOS include:

- **Meconium ileus** - Almost half of DIOS presentations are associated with a history of meconium ileus at birth [141,559,562]
- **Previous DIOS episode** - People with CF are up to 10 times more likely to develop recurrent DIOS post an initial episode [559]
- **Organ transplantation** [563-566]
- **CF-related diabetes and liver disease** – The relationship between these comorbidities is not a consistent finding across the literature [141,560]
- **Dehydration -** Most commonly associated with intercurrent illness. Ambient temperature peaks have also been found to play a potential role in the Australian context [234]

Malabsorption related to inadequate enzyme replacement resulting in unabsorbed fat in the distal ileum has previously been thought to be a predisposing DIOS risk factor due to delayed gastric emptying and transit time in CF [560]. However, recent studies have shown that this is unlikely to be the case [140-142].

The incidence of DIOS was previously thought to be higher in adults than children [567,568]. Since the release of the 2005 ESPGHAN definitions for constipation and DIOS in CF, recent studies have shown a similar incidence of DIOS in both the paediatric (6.2–7.7 episodes per 1000 patient-years) and adult (7.8 episodes per 1000 patient-years) population [141,559].

CONSTIPATION

Altered intestinal fluid composition, resulting from the primary CFTR defect is considered the main cause of constipation in CF [143]. Dysmotility and decreased water secretion in the intestine are also recognised as potential underlying mechanisms [569]. Unlike DIOS, genetic factors, including the severity of the CFTR genotype, are not thought to contribute to the incidence of constipation in CF [142,143,570].

Additional factors thought to contribute to constipation in CF:

- Low total fat absorption [143]
- Meconium ileus at birth [143]
- High ambient temperatures – hypothesised to result in intestinal intraluminal dehydration, thus increasing the risk of constipation [234]
- Medications - opiate analgesics, calcium and iron supplements and some antacids containing calcium or aluminum, list constipation as a common side effect

The impact of the following hypothesised risk factors for constipation in CF remains unclear:

- Poor fluid intake
- Inadequate fibre intake
- High dose pancreatic enzyme replacement therapy (PERT) - two papers report an association between high dose PERT and constipation [279,571] and one found no association [130]

While constipation is also a common occurrence in CF, only two studies have looked at constipation prevalence whereby it was found to range from 26-47% [143,572]. The incidence of constipation in CF is unknown.

Assessment

The potentially serious nature of DIOS should not be underestimated in CF. Differential diagnoses include constipation, appendicitis, appendicular abscess, Crohn's disease, adhesions, volvulus, intussusception, fibrosing colonopathy and malignancy [560]. Diagnostic investigations for CF patients presenting with acute abdominal pain usually include an abdominal x-ray and ultrasound [570].

DIET

While evidence to support the role of dietary factors in the development of either DIOS or constipation in CF is lacking, nutrition assessment should include a review of dietary intake including recent changes to pancreatic enzyme replacement therapy and sodium, fluid and fibre intake. Overall there is inadequate evidence to determine the role of nutrition in the prevention and management of DIOS.

What are the nutrition considerations for the prevention and management of Distal Intestinal Obstruction Syndrome (DIOS) in CF? PICO 11.2.1

[Grade C] Inadequate PERT, including poor adherence and under-dosing, is unlikely to play a role in DIOS but should still be assessed as part of an overall dietetics review in CF.

The impact of diet, particularly fibre and fluid intake on DIOS is unclear.

Further research in the Australian and New Zealand context, particularly in regards to the impact of hydration on DIOS is required. While not examined in the current body of evidence, the impact of sodium intake on hydration and DIOS is warranted in future research. [140-142]

What are the nutrition considerations for the prevention and management of constipation in Cystic CF? PICO 11.2.2

[Grade D] There is inadequate evidence to recommend nutrition considerations in the prevention and management of constipation in CF.

Until further evidence is available, complete a thorough diet history, including assessment of hydration (fluid and sodium intake) as well as fibre intake. Review PERT to optimise absorption.

Further research in the Australian and New Zealand context is warranted, particularly in regards to hydration (including sodium intake) and constipation in CF. [143]

While one study has found that sub-optimal fat absorption may contribute to constipation and that inadequate fluid and fibre intake do not, the evidence base is small and not applicable to the Australian and NZ context [143]. Overall there is inadequate evidence to determine the role of nutrition in the prevention and management of constipation in CF.

CLINICAL

Key nutrition related considerations for DIOS and constipation include:

- Nausea and vomiting
  - Distinguishing between bilious vs. non-bilious vomiting is important when differentiating between complete and incomplete DIOS
- Bowel patterns
  - Note any recent changes in frequency and/or consistency of bowel motions. A change in bowel habits, while usually present in constipation, may not always be a feature of DIOS
- Presence of overflow diarrhoea and/or faecal incontinence/soiling
- Presence of abdominal pain and distention
- Medications
  - Note medications with a known side effect of constipation (i.e. opiate analgesics and iron and calcium supplements)
  - Use of aperients (i.e. polyethylene glycol (PEG), Lactulose or Gastrografin)
  - PERT
  - Salt tablets
  - Adherence and any recent changes
- Recent intercurrent illnesses

The duration of all clinical symptoms should be noted.

BIOCHEMICAL & LABORATORY DATA

There are no routine biochemical markers for the assessment of constipation and DIOS in CF. In the event of DIOS, monitoring of electrolyte disturbances is warranted if dehydration occurs [573] Renal function should also be monitored as the patient is vigorously rehydrated. In the event of persistent constipation, alternate causes such as coeliac disease should be considered.

Intervention

DISTAL INTESTINAL OBSTRUCTION SYNDROME

Medical intervention is a priority for a patient presenting with acute abdominal pain and suspected DIOS. While treatment protocols vary between centres, most follow a stepwise approach [560]. Surgical intervention (ranging from surgical decompression to open laparotomy and resection) is rarely required for the management of DIOS [141,143,560,565].

Examples of paediatric and adult DIOS management flowcharts are outlined in Figure 11a [573] and Figure 11b [574]. These are site specific examples and practice may vary across sites, so it is important to refer to local guidelines.

CONSTIPATION

The treatment for constipation is usually intensive laxative treatment [143]. Whilst the role of diet in the prevention of constipation in CF is unclear, optimisation of hydration (fluid and salt intake) and pancreatic enzyme dosing and adherence is recommended. While not routine practice, a small dose of PERT, usually third hourly may be prescribed to avoid further obstructions in patients who are initially nil by mouth.

Monitoring & Evaluation

DISTAL INTESTINAL OBSTRUCTION SYNDROME

Dehydration and fat malabsorption should be avoided to prevent recurrence of DIOS [570]. Close monitoring of bowel patterns, fluid and salt intake as well as pancreatic enzyme replacement dosing and adherence is recommended for people with a history of DIOS. The ongoing use of aperients after an acute DIOS episode is common and should also be reviewed regularly [560,570].

CONSTIPATION

Thorough clinical review, with focus on stool patterns and medications, particularly aperients, is important when monitoring the often chronic complication of constipation in CF. While conclusive evidence is lacking, hydration status [234,572] and the prevention of fat malabsorption is recommended in the management of constipation [143].

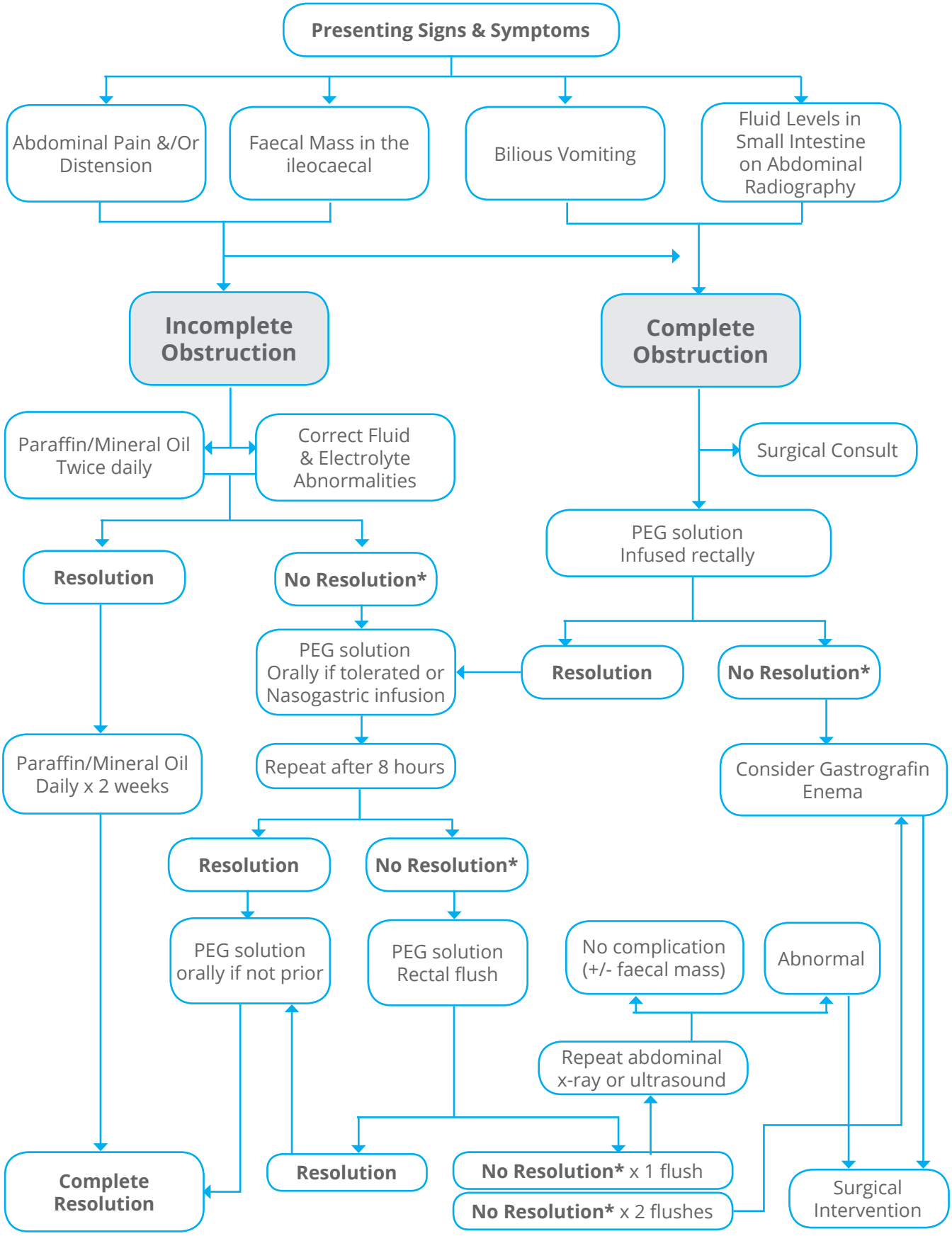

Figure 11a. Diagram outlining management recommendations at the Children's Hospital Westmead (Westmead, NSW, Australia).

* Low threshold for further imaging (abdominal x-ray and ultrasound)

[573] Note: Mineral oils should not be used for the treatment of DIOS & constipation in children less than 12 months of age.

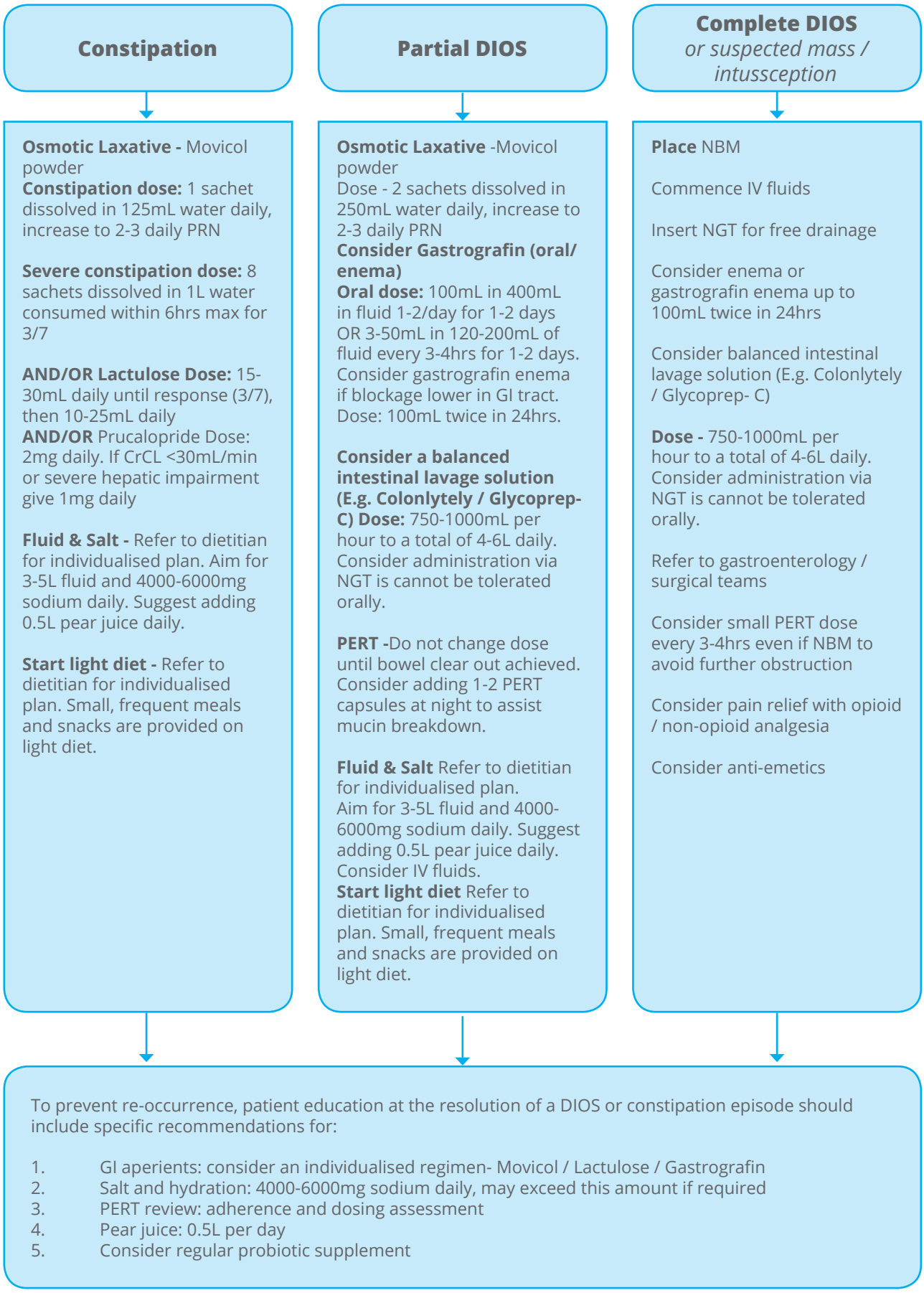

Figure 11b. Management recommendations at the The Prince Charles Hospital (Chermside, QLD, Australia) [574].

Practice Points PICO 11.2.1 and 11.2.2

- Medical treatment is a priority, particularly for the diagnosis and management of DIOS.
- Surgical intervention is rarely required.
- Polyethylene glycol (PEG) laxatives are usually used for the treatment of constipation and are often a first line treatment for DIOS. Many patients continue on laxatives after the resolution of DIOS.
- Optimise fluid and salt intake as well as fat absorption in those who present with or have a history of constipation and DIOS.
- Patients with complete DIOS may be fasted during initial treatment. In most cases this is short term, however, monitor patients for risk of malnutrition. Total parenteral nutrition (TPN) may be required for more complex cases that do not resolve in a few days.
- The Bristol stool chart can be used when assessing bowel patterns in CF. A paediatric version is also available when trying to engage younger children.

Laxatives:

- Insufficient evidence to assess the relative effectiveness or tolerability of different classes of laxatives. Considerations when choosing an agent should include hardness of the stool, potential adverse effects, effectiveness of previous treatments and patient preference.
- Adjust laxative regimens according to response and tolerability.
- Osmotic laxatives draw water into the stool to help soften the stool and washout the colon. The active ingredient in most osmotic laxatives is usually Polyethylene glycol (PEG). Lactulose, a non-absorbable sugar, is another osmotic laxative used in CF but is often associated increased abdominal pain/cramping.
- Stool lubricants help lubricate the bowel wall & soften faecal mass to allow the faecal mass to transit through the colon.

NOTE - Mineral oils should not be used for the treatment of DIOS & constipation in children less than 12 months of age. Potential side effects of longer term use in children greater than 12 months of age include:

- Possibility of reduced fat soluble vitamins.
- Abdominal cramps

Risk of aspiration if used during period of respiratory exacerbation or if the child is fighting the dose.

Translating into Practice

Tools used to assess gastrointestinal (GI) symptoms in CF may include:

- The Bristol stool chart
  - Stool form scale used to assess changes in intestinal function [575]
  - A modified version of the tool is readily available on the internet for the paediatric population
  - Not validated for the CF population so should be used in combination with other GI assessment tools or questions
- GI symptom trackers

There is currently insufficient evidence to assess the relative effectiveness or tolerability of different classes of laxatives. In practice, the choice of agent depends on symptoms, required onset of action, hardness of stool, potential adverse effects, effectiveness of previous treatments and patient preference. Regimens are then adjusted according to response and tolerability. Some examples of commonly used laxatives are as follows:

- Osmotic laxatives draw water into the stool to help soften the stool and washout the colon. The active ingredient in most osmotic laxatives is usually Polyethylene glycol (PEG). Products commonly used in CF include Movicol®, Osmolax® and GoLYTELY® in Australia or Kleanprep® in New Zealand. Lactulose, a non-absorbable sugar, is another osmotic laxative used in CF but is often associated with increased abdominal pain/cramping
- Stool lubricants, such as mineral oil (Parachoc® and Paraffin Oil®) help lubricate the bowel wall and soften faecal mass to allow the faecal mass to slide along easily

NOTE - Mineral oils should not be used for the treatment of DIOS and constipation in children less than 12 months of age. Potential side effects of longer term use in children greater than 12 months of age include:

- Possibility of reduced fat soluble vitamins
- Abdominal cramps
- Risk of aspiration if used during period of respiratory exacerbation or if the child is fighting the administration of the mineral oil

11.3 Colon Cancer Screening

Advancements in treatment options, early diagnosis and organ transplantation have led to an increased survival rate for people with CF. In turn, complications such as gastrointestinal malignancies have emerged. Colon cancer represents the highest risk in comparison with all other GI cancers for people with CF post transplantation [576].

Disease Aetiology

A recent study showed that people with CF had a higher rate of adenomatous polyps and a greater risk of developing colon cancer than the general population [577]. In all patients who had follow-up colonoscopies within one to three years, multiple polyps were found. The mechanism underlying the increased incidence of polyps has not been established. It has been suggested that it may be related to increased epithelial cell proliferation and turnover, and/or the altered composition of intestinal mucous, but further research is required [578].

There is limited evidence specific to colon cancer screening in CF. Further research is required into the type of preparation used. The standard bowel preparation used for the general population may result in inadequate clearance, poor gastrointestinal visualisation and lower detection rates in people with CF due to the intestinal secretions [578,579]. The optimal length and aggressiveness of CF-specific bowel preparations have yet to be agreed on.

Assessment

DIET

CF-specific colonoscopy preparation and recommendations (medications, doses and length of preparation) may vary. The preparation regimen, a decreased appetite and/or loose stools may impact the individual's ability to meet their nutritional requirements. This should be more closely assessed in the malnourished individual.

CLINICAL

Key points to consider as part of a clinical assessment include:

- Unexplained weight loss
- Unexplained abdominal pain
- Bowel obstruction unrelated to DIOS
- Rectal bleeding
- Family history of colorectal cancer

A colonoscopy is recommended as part of the screening process for colon cancer.

BIOCHEMICAL & LABORATORY DATA

The medical assessment and diagnosis of colon cancer involves a colonoscopy. CT colonography has not been assessed in the setting of CF.

Intervention

What are the nutrition considerations for colon cancer screening in CF? PICO 11.3.1

[Ungraded] There is insufficient evidence available regarding nutrition considerations for colon cancer screening in CF.

The following factors should be considered during preparation for colonoscopy:

- People at risk of malnutrition or diagnosed with malnutrition may consume clear fluid oral nutrition supplements containing protein
- Cordial, high energy cordial, lemonade or clear oral nutrition supplements may assist tolerance of the colonoscopy preparation. Alternatively, preparation administered via the nasogastric tube may be considered
- Monitor blood glucose levels and insulin requirements (especially in those people with CF-related or frequent hypoglycaemic episodes)
- Monitor hydration status and renal function

Monitoring and Evaluation

There is currently no consensus with regards to the age at which colon cancer screening may be warranted. After initial colonoscopy, gastroenterologists may recommend further surveillance every 1-5 years based on initial results, risk profile and the general population guidelines.

An increased survival rate in people with CF suggests that earlier colon cancer screening may be warranted. The Minnesota Cystic Fibrosis Centre screens all patients aged ≥40 years old [577]. Local CF centres should consider individualised colon cancer screening until further research and consensus is available.

A few reports have identified poor gastrointestinal visualisation [577,579] with standard colon preparation in CF compared to the general population. Further research is required to optimise colonic preparation solutions in this specific patient group.

Practice Points PICO 11.3.1

People with CF have a greater risk of developing colon cancer than the general population. Individual centres need to develop local guidelines with regard to screening older adults to assess risk of colorectal cancer

More extensive colonoscopy preparation may be required and further research is required.

11.4 Liver Considerations

There is a wide spectrum of manifestations that affect the hepatobiliary system in CF, including involvement of the liver, gallbladder and biliary tree [236]. CF-related liver disease is the third leading cause of death in CF [580]. While there is no universally accepted definition available, CF-related liver disease may present with neonatal cholestasis, asymptomatic elevation of liver enzymes, through to hepatic steatosis and focal biliary cirrhosis to the clinically relevant and more severe complication of multilobular cirrhosis [236]. The majority of people with CF do not go on to develop this severe complication of cirrhosis with portal hypertension [581], but those affected are at risk of variceal bleeding and progression to liver failure and need for transplantation, which increases the risk of morbidity and mortality [581,582]. Liver disease can have serious implications for the nutritional status of people with CF, i.e. increased risk of malabsorption, undernutrition/malnutrition and fat soluble vitamin deficiencies [233].

Disease Aetiology

CF-related liver disease often develops before or during adolescence, with ninety percent of severe disease being diagnosed by 20 years of age [581-583]. Liver disease almost universally affects people with CF who are pancreatic insufficient and have severe CF genotypes [581,584]. Male gender has also been suggested as a risk factor [581,582].

The cause of CF-related liver disease remains largely unidentified, although it is thought to be related to the CFTR gene which is expressed in the epithelium of the bile ducts [580]. Absence or dysfunction of CFTR likely causes the retention and accumulation of bile acids [580]. Accumulation of bile acids leads to hepatocyte injury, which in turn increases fibrogenic and pro-inflammatory cytokines expression, eventually resulting in peribiliary fibrogenesis [580,585,586]. Ongoing inflammation and hepatocyte damage results in fibrogenesis, progressing over time to multilobular cirrhosis [236].

The prevalence of CF-related liver disease is poorly described, partly due to the absence of a universally accepted definition and the lack of sensitive non-invasive diagnostic tests. Development of cirrhosis and portal hypertension occurs in five percent of patients with CF with clinically significant hepatobiliary manifestations reported to occur in 15 to 30 percent of children and adolescents [582]. Upon death, autopsy has revealed that approximately 70 percent of adults with CF have severe liver disease and in many cases this was not recognised antemortum [587].

Assessment

DIET

Assess dietary intake of energy, protein and essential fatty acids

- Cirrhosis leads to increased basal metabolic rate and energy requirements [588]
- Steatosis has been associated with malnutrition, and deficiencies of essential fatty acids, carnitine and choline [588]

- Large ascites can cause early satiety [589]
- Reduced appetites are common [589]
- Dietary intake is often over-reported by those with liver disease [589]
- Review fat soluble vitamin supplementation and pancreatic enzyme replacement therapy
- Liver disease may exacerbate the severity of malabsorption as a consequence of diminished bile acid secretion and/or circulation (i.e. cholestasis) [144]. Further increasing the risk of fat soluble vitamin deficiencies.
- People with CF can develop cholestasis, otherwise known as conjugated hyperbilirubinaemia (e.g. during infancy, and at end stage of decompensated chronic liver disease)

CLINICAL

Presentation of CF-related liver disease is often subclinical with many remaining asymptomatic until the pathological changes are diffuse and pronounced [144]. Signs and symptoms of people with portal hypertension[2*] and multilobular cirrhosis include [590]

HYPERSPLENISM

- Oesophageal or gastric varices
- Ascites
- Synthetic liver failure[3*] (rare) [591]
- Difficulty in gaining and maintaining weight

Clinical presentation of severe liver disease may include [590]

- Fatigue
- Nausea
- Abdominal distension and/or pain

ANTHROPOMETRY

The presence of ascites will confound anthropometric data with regards to measurement of weight and BMI, potentially causing overestimation of nutritional status [589]. Use of mid arm circumference and skin fold measurements may be more appropriate anthropometric variables for people with severe liver disease as they do not require adjustment or interpretation for hydration [589]. Hand-grip strength can also be a good functional assessment tool for liver patients, however this has not been validated in CF [589].

MEDICAL SCREENING AND DIAGNOSIS

Screening consists of annual liver transaminase measurement; if the levels are elevated, an abdominal ultrasound is obtained and done annually thereafter if cystic fibrosis–related liver disease is suspected. The risk of gallstones is also higher in cystic fibrosis [592]. Liver biopsies are not routinely obtained in CF-related liver disease unless another diagnosis is being considered that would change management [236]. Furthermore, cystic fibrosis–related liver disease is patchy and can be missed on routine liver biopsy [592].

BIOCHEMICAL & LABORATORY DATA

ELEVATIONS IN LIVER FUNCTION TESTS

Biochemical abnormalities are common in patients with CF. Results vary over time and may be absent even in those with advanced cirrhosis [580]. Elevated alanine aminotransferase (ALT), aspartate aminotransferase (AAT) or gamma-glutamyl transferase (GGT) may be seen but none are predicative or indicative of severe CF-related liver disease [593].

FAT-SOLUBLE VITAMINS

The presence of liver disease can make accurate assessment of fat soluble vitamin levels challenging and less clear, because it is the liver that is responsible for producing the biochemical markers used in assessment, and it also is the primary location where large amounts of fat soluble vitamins are stored. Chapter 8 describes management of fat soluble vitamins in more detail.

- **Vitamin A:** Monitor serum retinol together with retinol-binding protein (RBP) to ensure appropriate therapy to prevent deficiency, as well as fasting serum retinyl ester concentration to assess for toxicity [78,144,202,252]. Calculation of retinol : retinol binding protein ratio will provide further insight into vitamin A status and the appropriateness of management. Calculation is outlined in Chapter 8.

2 * *Portal hypertension may predate the onset of cirrhosis in some people with CF.*

3 * *Only 10 percent of people with CF will progress to loss of synthetic liver function characterised by a high bilirubin and vitamin K resistant coagulopathy.*

- **Vitamin D:** Assess serum 25-hydroxyvitamin D
- **Vitamin E:** Including a serum vitamin E : total lipid ratio is particularly important when interpreting vitamin E status in liver disease [363,365,402] . Vitamin E deficiency may be missed if lipids are not considered [402].
- **Vitamin K:** The risk of vitamin K deficiency is increased in people with CF-related liver disease. Prothrombin time is an insensitive measure of vitamin K, and is generally only indicative of severe deficiency. The PIVKA-II (protein induced vitamin K absence-IICF-related liver disease) test is a more sensitive measure of detecting vitamin K deficiency than prothrombin time and reflects vitamin K deficiency of the liver, however is not readily available [365,408].

Intervention

Interdisciplinary input into the management of CF-related liver disease is essential (physician, dietitian, and pharmacist), ideally being overseen by a gastroenterologist. Treatments for liver disease remain supportive in nature; namely, optimisation of nutritional status and early identification/management of complications.

NUTRITIONAL SUPPORT

Should vitamin K supplementation be recommended for all people with CF-related liver disease? PICO 11.4.1

[Ungraded] Insufficient evidence to make a recommendation – follow recent consensus guidelines. [144]

Practitioners should be guided by the most recent recommendations for vitamin K supplementation in CF. The European consensus guidelines for the management of CF-related liver disease, suggest that daily supplementation of Vitamin K for children and adults is recommended [78,144]. Routine daily supplementation for people with pancreatic insufficiency is as follows:

- Infants: 300-1000 µg/d
- Children (>1year): 1000-10 000 µg/d
- Adults: 1000-10 000 µg/d

What are the requirements for effective supplementation in episodes of vitamin A deficiency in people with CF-related liver disease? PICO 11.4.2

[Ungraded] Insufficient evidence to make a recommendation – follow recent consensus guidelines. [144]

In the absence of evidence clinicians should be guided by the most recent consensus guidelines which suggest that high oral doses (5000 to 15 000IU/day) of vitamin A may be required to attain adequate vitamin A status in people with CF-related liver disease [144]. Careful monitoring of biochemical data to prevent vitamin A toxicity or deficiency is also recommended [144].

The following nutrition strategies are highlighted in a recent expert-opinion based guideline [144]:

- Use nutritional support interventions to achieve optimal growth in children and weight in adults with CF-related liver disease :
  - Increase the proportion of fat in the diet and/or supplementary enteral feed to 40 to 50 percent of total energy intake.
  - Supplementation with medium chain triglycerides and use of polyunsaturated fatty acids may provide benefit to some people with CF-related liver disease
  - Caution with excessive use of carbohydrate supplements (e.g. glucose polymers) due to the risk of development of CF-related diabetes [594]
- The supply of protein should not be routinely restricted, unless there are signs of decompensated liver failure and hepatic encephalopathy.
- Optimise use of pancreatic enzyme replacement therapy to enhance absorption of long-chain triglycerides and essential fatty acids.
- Avoid excess supplementation of salt in the presence of cirrhosis and portal hypertension to reduce the development of ascites.

PHARMACOLOGICAL AND MEDICAL INTERVENTIONS

Ursodeoxycholic acid is often used to treat CF-related liver disease and can result in normalisation of liver transaminases, but there is currently no evidence to support its use for the treatment or prevention of cirrhosis with portal hypertension in CF [595]. Concerns about its safety have also been raised [596]. As such, this is not a routinely recommended treatment.

LIVER TRANSPLANT

The best practice guidelines for the diagnosis and management of CF-related liver disease outline indications for liver transplantation in CF [144]. The 2014 Australian Data Registry report describes one person with CF being accepted for a liver transplant in 2014 [188]. Close liaison between the CF team and the liver transplant team is essential to ensure optimal patient management.

Monitoring & Evaluation

Weight, body mass index, lung function, and vitamin status should be monitored regularly. All CF patients with liver disease require annual follow-up by gastroenterologist to evaluate the progression to cirrhosis and monitor for development of portal hypertension and other complications [144].

Practice Points PICO 11.4.1

The risk of vitamin K deficiency is increased in people with CF-related liver disease. Clinicians should base supplementation on the most recent recommendations for vitamin K supplementation in CF *[78,144]:*

- Routine daily supplementation for all PI patients
- Infants: 300 – 1000µg/d
- Children (>1year) and adults: 1000 - 10 000 µg/d

Practice Points PICO 11.4.2

Supplement with high oral doses between 5000 – 15 000IU/day (1500ug - 4500 µg/d) with the aim of achieving the normal range of serum retinol for healthy individuals.

Use caution when giving doses above 20 000 IU/d (6000 µg/d) preformed vitamin A if RBP is low. A low retinol : RBP molar ratio may indicate deficiency but further increase in supplementation of preformed vitamin A may be toxic to the liver. Although not routinely available we recommend increased supplementation with β-carotene in these circumstances.

Monitor serum retinol and retinol binding protein to ensure the adequacy of therapy to prevent deficiency as well as fasting serum retinyl ester concentration to assess for toxicity.

11.5 Additional GI considerations & the role of the Gastroenterologist

Cystic fibrosis has wide-ranging effects on the gastrointestinal tract. In addition to the conditions described above, other common conditions and/or clinical manifestations of CF should also be considered. These include delayed gastric emptying, intestinal dysbiosis and infection, intestinal inflammation, intussusception and appendiceal disease.

GASTROPARESIS

The dysmotility that affects the gastrointestinal tract in CF may also involve the stomach. However, delayed gastric emptying (or gastroparesis) is not a consistent finding, with gastric emptying reported to be accelerated [495], normal [496] and delayed [497] in patients with CF when compared to general population controls. Patients may report

symptoms of reduced appetite, nausea or early satiety. Affected patients may also present with symptoms similar to gastroesophageal reflux (e.g. recurrent vomiting). Gastroparesis may impact on oral caloric intake and nutritional status, glycaemic control, and also interfere with efficacy of pancreatic enzyme replacement therapy [111]. There is currently no "gold" standard for the diagnosis of gastroparesis. Various techniques have been used to measure gastric emptying (e.g. technetium scintigraphy [495], C-Octanoic breath test) [111] and different test meals (solid vs. liquid) have been used. There is also a lack of validated reference ranges in certain age groups for the various techniques and test meals. Prokinetics and dietary modification is recommended for the management of gastroparesis [597,598]. In terms of dietary modifications, fat and fibre are known to delay gastric emptying, so limiting these sources may be beneficial [597]. Enteral nutrition support should be considered if oral intake is found to be insufficient. An initial trial of continuous or small volume bolus gastric feeding (nasogastric or gastrostomy) should be considered. Failing this, continuous trans-pyloric feeding (jejunostomy or naso-jejunal feeding) is the next consideration [597].

INTESTINAL DYSBIOSIS

Intestinal dysbiosis, historically referred to as small bowel bacterial overgrowth (SBBO), is another well-reported complication of CF [236]. SBBO may present with non-specific symptoms of abdominal pain, bloating, weight loss, diarrhoea and steatorrhoea. In addition, SBBO has been implicated with the development of intestinal inflammation in CF [236]. Treatment of SBBO involves the use of enteric antibiotics, with different antibiotic regimens proposed [599]. The role of probiotics in restoring the gut microbiota remains to be fully explored (Chapter 15).

INTUSSUSCEPTION

Intussusception occurs 10-20 times more frequently in patients with CF compared to the general population [600], however cases in CF remain uncommon. It is hypothesised that the adherent inspissated muco-faeculent material on the intestinal mucosa acts as lead point. Intussusception may present with symptoms of bowel obstruction, abdominal mass on abdominal palpation and poses the risk of intestinal ischaemia in the affected intestinal segment if missed. The differential diagnoses of DIOS, appendicitis and gastrointestinal cancer should also be considered. Similarly, a delayed diagnosis of appendicitis is reported in patients with CF [600].

OTHER GASTROINTESTINAL ENTEROPATHIES

Whether there is an increased prevalence of co-existing enteropathies such as inflammatory bowel disease (IBD) and coeliac disease among patients with CF is controversial. Previous reports indicate up to 17- and 3-fold increase in prevalence of Crohn's disease and coeliac disease respectively in the CF population [601,602]. However, none of these studies have been replicated elsewhere. It remains unclear whether the initial reports of increased prevalence of IBD in CF were related to fibrosing colonopathy rather than true IBD [603]. Nonetheless, refractory gastrointestinal symptoms should prompt a referral to gastroenterologist for further evaluation.

CHAPTER 12 CYSTIC FIBROSIS RELATED DIABETES

A. Matson & T. Katz

CF-related diabetes shares features of type 1 and type 2 diabetes but is a distinct form of diabetes classified as "other forms of diabetes" or pancreatogenic diabetes [145,146]. This form of diabetes occurs at the end of a spectrum of progressive glucose tolerance abnormalities; it may occur intermittently, and few people with CF demonstrate completely normal glucose tolerance [147,148].

Comparison bewteen type 1 and type 2 diabetes and CF-related diabetes has been summarised in clinical reviews [604,605]. Type 1 diabetes arises from β-cell destruction primarily due to autoimmune aetiology with islet cell antibodies (ICA), glutamic acid carboxylase (GAD) or tyrosine phosphatase (1A-2A) antibodies present in 85% of cases [606]. CF-related is not an autoimmune condition (no autoimmune antibodies are present) , hence if a patient presents acutely with polyuria, polydipsia, lethargy, weight loss, hyperglycaemia, blood and urinary ketones; patients should be tested for the rare occurrence of type 1 diabetes co-occuring with cystic fibrosis by testing for autoimmune antibodies.

As the CF population increases in age, those with milder disease who are pancreatic sufficient and possibly overweight may also experience age related β-cell decline (and / or islet destruction secondary to pancreatitis), this may obscure the distinction between type 2 diabetes and CF-related diabetes [604]. Treatment should be tailored towards the individual in these cases aiming to improve BMI, glycaemia, lipidaemia and hypertension.

Prior to the clinical diagnosis of CF-related diabetes, abnormal glucose tolerance may adversely impact on pulmonary function and nutritional status with many studies demonstrating increased morbidity and mortality, especially in females [239]. If not recognised, or inadequately controlled, diabetes can contribute to energy deficits through glycosuria and loss of protein anabolism from insulinopaenia [607,608].

Less mortality has been observed in people with CF and CF-related diabetes with screening by annual two hour oral glucose tolerance tests (OGTT) from age 10, and early commencement of insulin therapy [145,609]. Insulin management has also been observed to reverse a decline in lung function and BMI in individuals with CF [238,610,611]. Despite these improvements, research to enhance understanding of optimal screening, diagnosis and treatment practices for early detection and management of CF-related diabetes is ongoing.

It is important to note that the methodology used to create this chapter is different from the rest of the guideline document. Data from the 2 most recent Australian and NZ CF dietitian surveys [180,612] indicates that practice in managing CF-related diabetes is amongst the most inconsistent. In an attempt to improve consistency of practice where possible (and rather than performing a full systematic review), existing guideline paper recommendations have been emphasised when they are applicable to the Australian and NZ context.

Disease Aetiology

The primary defect in CF-related diabetes is reduced β-cell mass leading to insulin deficiency, in part caused by fibrosis of pancreatic cells due to the CFTR defect. More recently the CF mutated gene has been identified as having a role in regulating insulin secretion in beta cells [613], a function that can be recovered by those treated with Ivacaftor [614]. Insulin resistance, especially during periods of acute illness, in patients with liver disease, during pregnancy and when prescribed systemic glucocorticoids may also play a causal role. Genetic variants for type 2 diabetic susceptibility genes have also been linked with development of CF-related diabetes [615]. Further research continues into the pathophysiology of CF-related diabetes.

Prevalence of CF-related diabetes increases with age and affects approximately 50% of people with CF by the age of 40 [238,615]. The 2014 Australian Data Registry reported on the rates of chronic CF-related diabetes requiring insulin as:

- young and older children - 6.8%
- adolescents - 26.7%
- adults (>30 years) - 27.2% [188]

Recent data from NZ reports a slightly higher prevalence (8.6%) in children under 11 years of age [189].

Centres not routinely performing annual OGTT screening may underestimate the prevalence of CF-related diabetes [616]. People with severe CF disease, pancreatic insufficiency and Type 2 Diabetes susceptibility genes may have greater incidence of CF-related diabetes, although pancreatic sufficient individuals can also be affected [617].

Comparison of type 1 and type 2 diabetes and CF-related diabetes has been summarised in clinical reviews [604,605]. Type 1 diabetes may be differentiated from CF-related diabetes by testing autoimmune antibodies, although rare type 1 diabetes and CF can co-exist. Type 2 diabetes may occur in people with CF and pancreatic sufficiency, those at risk are overweight individuals with metabolic syndrome and treatment should be individualised.

Assessment

DIET

At CF-related diabetes diagnosis a complete nutritional assessment should be undertaken as per Chapter 5 and the Australian CF standards of Care Recommendations [2]. The dietary assessment should be conducted within the context of overall health, lifestyle, exercise and eating patterns. Particular focus should assess the quantity (e.g. grams of carbohydrate consumed at usual meals / snacks / supplements) and quality of carbohydrate intake (the glycaemic index (GI)) at meals and snacks. The blood glucose levels pre-meal and 2 hours post-meals should be assessed to assist with planning an insulin regimen with the Endocrinologist and planning diet modifications.

Pancreatic enzyme replacement therapy (PERT) should be assessed as described in chapter 10. Maximising PERT efficacy has been demonstrated to improve glucose excursions [618].

CLINICAL

CF-RELATED DIABETES SCREENING

Screening for CF-related diabetes has been demonstrated to reduce morbidity and mortality rates by enabling early identification and intervention [145,609].

During a time of clinical stability (at least 6 weeks since an acute exacerbation, after an 8 hour fast, and consumption of 150g carbohydrate /d for 3 days prior to the OGTT), routine screening should be performed using a 2 hour OGTT with 75g of oral glucose (or 1.75g/kg in children) with blood glucose measures taken at 0, 1 and 2 hours [238,615,619]. The glucose dose can be given via gastrostomy if more acceptable.

Exceptions to screening with OGTT are an individual with CF presenting with classical symptoms of polyuria and polydipsia in the presence of a glucose level >11.1 mmol/l or an individual with CF having two more diagnostic criteria for diabetes (such as both fasting and 2-h glucose elevation or a diabetes pattern on OGTT in the presence of a HbA1C level >6.5%).

Glycosylated haemoglobin (HbA1c) is not recommended for routine screening, as HbA1c may be lower in patients with CF possibly due to increased red blood cell turnover and inflammation [238,615,619]. Recently Burgess et al (2016) suggested the use of HbA1c greater than or equal to 5.8% as a quick CF-related diabetes screening tool [620], however concern has been expressed in patients with advanced CF lung disease [621,622] due to the risk of insulinopaenia and the risk of failing to identify patients with early glucose abnormalities by relying on this method. Research continues as to the optimal early diagnosis criteria and management strategies specifically related to CF-related diabetes.

Table 12a. Screening considerations for people not known to have CF-related diabetes*

	Considerations
Routine screening	During a time of clinical stability (at least 6 weeks since an acute exacerbation, after an 8 hour fast, and consumption of 150g carbohydrate /d for 3 days prior to the OGTT) a 2 hour OGTT with 75g of oral glucose (or 1.75g/kg in children) with BGLs measured at 0, 1 and 2 hours should be performed. Annual screening for CF-related diabetes should begin by age 10 in all people with CF. Children < 10 years of age should only be screened if clinically indicated e.g acute loss of lung function and / or weight, symptomatic polyuria, polydipsia, or hyperglycaemia on routine blood testing.
Illness	In those with acute pulmonary exacerbation requiring intravenous antibiotic and/or systematic glucocorticoids, the risk of hyperglycaemia is increased. People with CF who are unwell may develop hyperglycaemia intermittently. Fasting and 2hr post prandial plasma glucose levels should be checked for the first 48 hours of admission.

...table continued overleaf

Enteral feeding	To maximise provision of high caloric enteral feeds in malnourished individuals with CF and to assist weight gain, screening for BGLs >11.1 mmol / l is advised. Plasma glucose levels should be checked once midway through feed provision and immediately post feeds. This should occur at the time of gastrostomy tube insertion and then monthly.
Pregnancy (Chapter 14)	Women with CF who are planning a pregnancy or confirmed to be pregnant should be screened for pre-existing CF-related diabetes if they have not been screened in the previous 6 months. Screening for gestational diabetes via a 2 hour OGTT is recommended at both 12-16 week and 24-28 weeks of gestation in pregnant women with CF not known to have CF-related diabetes. Post pregnancy screening for CF-related diabetes is recommended 6-12 weeks post-partum for those who had gestational diabetes.

*Adapted from [238,615,619]

CF-RELATED DIABETES DIAGNOSIS

The most current criteria for the diagnosis of CF-related diabetes based on the 2014 *'International Society for Diabetes and Adolescent Diabetes (ISPAD) clinical practice consensus guidelines: management of CF-related diabetes in children and adolescents'* [238] is summarised in table 12b with considerations for diagnosis under various circumstances shown in table 12c. Various Australian and international guidelines recommend an annual formal fasting 75 gram 2 hour OGTT (or 1.75g/kg in children) to screen for and diagnose diabetes [615,623].

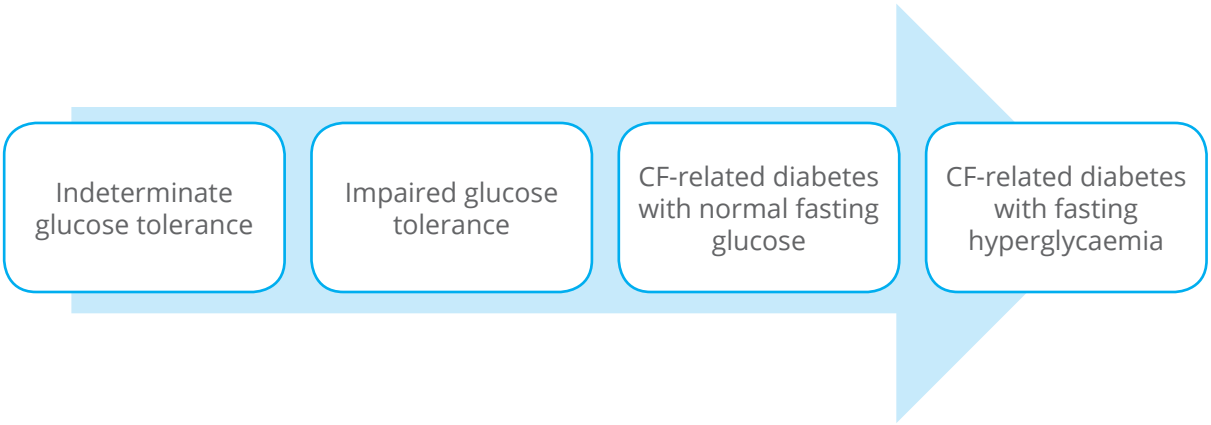

Figure 1. Diabetes in CF is part of a progressive spectrum of glucose tolerance abnormalities

Table 12b. Diagnostic criteria* for glucose abnormalities in individuals with CF

Category	Fasting plasma glucose (FPG) (mmol/L)	1 hour plasma glucose (mmol/L)	2 hour plasma glucose (mmol/L)
Normal glucose tolerance	< 7.0	-	< 7.8
Indeterminate glucose tolerance	< 7.0	≥ 11.1	< 7.8
Impaired glucose tolerance	< 7.0	-	7.8 - < 11.1
CF-related diabetes without fasting hyperglycaemia	< 7.0	-	≥ 11.1
CF-related diabetes with fasting hyperglycaemia	≥7.0	-	-

* Adapted from [238,615]

Table 12c. Considerations* for CF-related diabetes under various circumstances

Diagnostic criteria and considerations	
Clinical stability (healthy baseline)	Diagnosis is based on one or more of the following criteria at a time of clinical stability: • 2hr OGTT plasma glucose with a 120min BGL ≥11.1mmol/L • Fasting plasma glucose levels ≥7mmol/L • HbA1c ≥6.5% • random glucose measures ≥11.1mmol/L with symptoms of polyuria and/or polydipsia The first 3 measures listed above should be repeated on 2 separate days to confirm diagnosis.
Acute illness	Diagnosis may be made on one (or more) of the following criteria: • Fasting plasma glucose levels ≥7mmol/L • 2 hour post prandial plasma glucose levels ≥11.1mmol/L Either type of hyperglycaemia must persist more than 48 hours. An OGTT is not necessary as plasma blood glucose levels at the fasting and / or 2 hours post prandial time points may be used diagnostically during acute illness. CF-related diabetes diagnosed at this time may be intermittent or long term.
Enteral Feeding	Diagnosis made when blood glucose levels are ≥11.1mmol/L mid or immediately post enteral feeding on two separate days. • confirm via laboratory plasma glucose measurement • CF-related diabetes may occur in relation to the high carbohydrate load of an enteral feed; an OGTT will not identify this and hence plasma blood glucose mid or post feed can be used to make this diagnosis.
Pregnancy (Chapter 14)	Women with CF are at increased risk of gestational diabetes mellitus. Gestational diabetes is diagnosed using lower glycaemic thresholds of a 2 hour OGTT and is based on one or more of the following criteria • Fasting plasma glucose levels ≥5.1mmol/L • 1 hour plasma glucose ≥ 10mmol/L • 2 hour plasma glucose ≥ 8.5mmol/L

*adapted from [238,615,619,624,625]. Point of care capillary blood glucose (e.g. glucometer) is not recommended for screening/diagnosing diabetes.

CF-RELATED DIABETES AND HYPOGLYCAEMIA

Insulin induced hypoglycaemia can occur in CF-related diabetes as in any other patient on insulin therapy. However, hypoglycaemia (BGL less than or equal to 3.9 mmol/l or low enough to cause symptoms) is also recognised as a phenomenon in people with CF in the absence of diabetes or glucose lowering medications [615,626]. Fasting hypoglycaemia may reflect malnutrition and/or increased energy needs due to inflammation and infection [627]. Reactive or postprandial hypoglycaemia may be related to delayed or disordered insulin secretion.

Non CF-related diabetes hypoglycaemia is generally mild because patients have poor glucagon response to hypoglycaemia [628] but have a brisk catecholamine response [628] and normal hypoglycaemia awareness. Limited research on hypoglycaemia in the absence of diabetes or glucose lowering medications has been published, and further research is crucial to understanding the aetiology and management strategies to assist treatment.

CF-RELATED DIABETES AND DIABETIC KETOACIDOSIS

Diabetic ketoacidosis is uncommon in people with CF and thus, ketones are not routinely measured. [615]. If an individual with CF presents with diabetic ketoacidosis they should be screened for auto-immune antibodies to exclude type 1 diabetes mellitus occurring concurrently with CF e.g. islet cell antibodies (ICA), glutamic acid carboxylase (GAD) or tyrosine phosphatase (1A-2A) antibodies.

BIOCHEMICAL AND LABORATORY DATA

The biochemical criteria for the medical diagnosis of CF-related diabetes are outlined in tables 12b and 12c above.

Intervention

CF-related diabetes should be managed by an interdisciplinary team with knowledge in CF, including but not limited to an endocrinologist, CF physician, credentialed diabetes educator (CDE), dietitian, nurse and psychologist. The diabetes team should be familiar with CF-related diabetes, recognising the differences between this and Type 1 and 2 diabetes pathophysiology and treatment. Good communication between diabetes and CF care providers is essential [615].

MEDICAL MANAGEMENT

Principal goals in management of CF-related diabetes are symptom control, optimisation of nutritional status and lung function, avoidance of hypoglycaemia and hyperglycaemia, prevention of microvascular diabetic complications and psychological support to manage CF-related diabetes in combination with complexities of CF management. Table 12d provides an illustrative example of BGL treatment targets.

Insulin is the treatment of choice as the primary problem in CF-related diabetes is insulin insufficiency [238,615,619]. Oral diabetic agents are not currently recommended except as part of research trials [238,615].

Insulin is the only recommended medical treatment for CF-related diabetes with options for insulin delivery being single or multiple insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII) via an insulin pump. Insulin regimen decisions are based on achieving normo-glycaemia, balanced with patient acceptance of the insulin regimen.

There are no guidelines regarding the use of insulin pump therapy in treatment for CF-related diabetes, however a number of case reports and non – randomised studies [629] have reported improvement of glycaemic control and quality of life from insulin pump therapy. Pump therapy in CF-related diabetes management is not as widely used compared to as in type 1 diabetes [630], however this may change over time. Individuals should consult with their care teams regarding eligibility for insulin pump therapy and specialist management services available.

Table 12d. Example of treatment targets and goals for individuals with CF-related diabetes*

	Optimal Control	**Modified Control** (people at high risk of hypoglycaemia)	**Symptomatic Control** (when end-stage CF care is appropriate)
Fasting glucose	4-6 mmol/L	4-7 mmol/L	No BGL targets. Avoidance of hypo / hyperglycaemia for comfort measures are assessed on an individual basis.
2hr post meal glucose	4-7 mmol/L	7-10 mmol/L	No BGL targets. Avoidance of hypo / hyperglycaemia for comfort measures are assessed on an individual basis
Hypoglycaemia	Mild daytime hypos only	Aim for none	No BGL targets. Avoidance of hypoglycaemia for comfort measures are assessed on an individual basis
HbA1c	<7%	<8%	no HbA1c targets

*adapted from [631,632]

Medical management and insulin requirements may vary in some situations, and should be designed for the individual, in conjunction with relevant expert management teams

- **Enteral feeds -** extra insulin may be required during feeding sessions to cover the carbohydrate load, improve glycaemia and promote weight gain. Additional blood glucose monitoring before, during and after enteral nutrition will assist in determining the effects of enteral feeding on glycaemia and how best to adjust the insulin regimen.
- **Post lung transplant -** it is common for those post lung transplant to have changing nutritional and insulin requirements [238]. Refer to Chapter 16 for further information.
- **Genetic potentiator treatments (e.g. Ivacaftor) -** nutritional requirements may change and / or insulin secretion may improve [163]. Genetic potentiators are discussed in Chapter 14.
- **Exacerbations and infections -** acute illness may increase the risk of hyperglycaemia and insulin requirements may increase up to four times that required normally. Insulin doses must be reduced as the individual improves clinically to avoid hypoglycaemia, this may take a couple of months [238].

- **Pregnancy -** women with established CF-related diabetes, who are planning a pregnancy, or who are already pregnant, should optimise blood glucose control in accordance with advice from specialist endocrine and obstetric teams [633]. The Australasian Diabetes in Pregnancy Society (ADIPS) has recommended BGL targets at fasting, one and two hours post prandial, as follows [625]: Refer to Chapter 14 for further information.
    - Fasting capillary BGL: ≤5.0 mmol/L
    - 1 hour after commencing meal BGL: ≤7.4 mmol/L
    - 2 hours after commencing meal BGL: ≤6.7 mmol/L

Registration with the National Diabetes Service Scheme (NDDS) in Australia provides subsidised products (test strips, syringes, and pen needles) for diabetes requiring insulin and caused by CF. Registered medical and nurse practitioners, and credentialed diabetes educators can certify the NDSS form. Currently in Australia, continuous subcutaneous insulin infusion (CSII) via insulin pumps and related consumable products are government funded only for type 1 diabetes or available at full or subsidised cost through some private health funds. Individuals should contact their private health provider for eligibility criteria and discuss suitability with their Diabetes / CF health care teams.

In NZ Pharmac funds all products for diabetes management including CSII insulin pumps and consumables and registration is not required. International recommendations state that people with CF-related diabetes should be commenced on an individually tailored insulin regimen guided by the degree of glucose tolerance, eating habits and lifestyle [631,634-637]. There is no evidence that one type of insulin is superior to another.

SELF-MANAGEMENT OF CF-RELATED DIABETES

Practitioners should provide ongoing self-management education that meets national standards e.g. Australian Diabetes Educator Association guidelines and standards [638]. Education should include [639]:

- Self-monitoring of blood glucose
- Medications (i.e. insulin actions, timing, side effects, interactions)
- Relationship between CF-related diabetes and other health problems (e.g. weight, lung function, corticosteroids, sick days)
- Nutrition education as appropriate
- Carbohydrate counting as appropriate
- Exercise considerations
- Alcohol education
- Hypoglycaemia prevention and management, including use of glucagon

Self-monitoring of blood glucose levels should occur to assist in reviewing management goals [238,615]. Whilst establishing an insulin regimen, monitoring pre and 2 hours post prandial blood glucose levels provides information to assist insulin adjustment. Once established on an insulin regimen, pre-prandial and before bed time monitoring is usually sufficient to review blood glucose targets.

MEDICAL MANAGEMENT OF IMPAIRED GLUCOSE TOLERANCE

Small studies to treat indeterminate glucose tolerance and impaired glucose tolerance have demonstrated benefits in the early introduction of insulin [238]. Australian research has also demonstrated improved weight gain and lung function following once daily insulin treatment in these sub-population groups [640]. However, at present no definitive data has been published and this research area is of high priority.

NUTRITIONAL MANAGEMENT OF CF-RELATED DIABETES

There are currently no randomised controlled diet intervention trials in the management of CF-related diabetes. Recommendations are based on cohort studies and current clinical consensus guidelines [145,238,609,615,619]. A CF- related diabetes diagnosis does not alter usual CF dietary recommendations, the goal is to achieve and maintain good nutritional status and optimise blood glucose levels. A comparison between dietary considerations for people with Type 1 and 2 diabetes and CF-related diabetes is outlined in table 12e.

Specific energy and macronutrient considerations in CF-related diabetes compared to type 1 / type 2 diabetes include:

- **Energy** - whilst dietary restrictions are common in Type 1 and 2 diabetes, the majority of people with CF-related diabetes require higher energy intakes of 110-200% of the general population targets [619]. Energy requirements are reviewed in Chapter 7.

- **Protein** - protein requirements are 15-20 percent of total energy requirement and are discussed in Chapter 7.
- **Fat** - fat intake from all sources is usually not restricted in CF-related diabetes compared to type 1 and 2 diabetes. Quality and quantity of total fat intake should be individualised based on age, BMI and overall health status. See chapter 7 for further information.
- **Carbohydrate** – the high energy requirements of CF, combined with individual preference, somtimes demand the inclusion of refined sugars such as sweet foods and beverages. These foods should be as part of a meal or substantial snack as they can cause rapid rises in blood glucose if eaten in isolation [631]. Hyperglycaemia is known to perpetuate B-cell destruction hence diet related glucose elevations should be minimised by diet modification (the reduction and / or spreading of refined sugars throughout the day, and /or inclusion with mixed meals rather than eaten alone). When malnutrition necessitates the inclusion of refined sugar products, insulin therapy should be adjusted to match bolus insulin dose to the refined sugar carbohydrate quantity. Where possible, carbohydrate foods with low glycaemic index should be encouraged and distributed evenly and consistently throughout the day to help optimise blood glucose control, provided that these changes do not cause an unwanted reduction in the total caloric intake. A flexible dietary intake can be managed by altering the insulin dose using individually determined insulin to carbohydrate ratios [634].

Table 12e: Comparison of dietary management between type 1 and 2 diabetes in the general population and CF-related diabetes

Nutrient	Type 1 & 2 diabetes	CF-related diabetes
Energy (calories)	Individualised for growth, weight maintenance or reduction. To prevent overweight and obesity caloric restriction of <100% of normal requirements for age and gender may be used.	Individualised for growth, weight maintenance or reduction. Usually require 110-200% of normal caloric intake for age and gender to prevent undernutrition.
Protein	15-20% of total energy from protein Reduce to 0.8-1g/kg with nephropathy	15-20% of total energy from protein
Fat	<35% total energy from fat <7% total energy from saturated fat	Unrestricted: adequate fat to meet energy targets No restriction on type of fat
Total Carbohydrate	Individualised. Monitor to achieve glycaemic control. Total energy approximately 45-60% from carbohydrate. Artificial sweeteners may be used to assist glycaemic control and/or weight management in overweight/obese people.	Individualised. Monitor to achieve glycaemic control. Total energy approximately 45-65% from carbohydrate. Artificial sweeteners may be used to assist glycaemic control and / or weight management in overweight / obese people.
Dietary Fibre	Approximately 30g per day	Encouraged in the well-nourished CF population but not at the expense of other nutrients.
Salt	Restriction to approximately <2300mg per day for control of hypertension.	No restriction. Sodium requirements for CF are discussed in chapter 9.

Carbohydrate intake plays an important role in management. In addition to the advice provided around general dietary intake, as outlined in chapter 7, basic education on carbohydrate intake and recognition is required. People with CF-related diabetes should also be advised how they can integrate insulin regimens (i.e. taking into consideration the amount and distribution of carbohydrates) into their usual eating patterns and physical activity habits. For some people it may be appropriate to provide complex education regarding individualised insulin to carbohydrate ratios to assist in glycaemic control and carbohydrate counting skills.

Monitoring and evaluation

People with CF-related diabetes require review from a diabetes perspective at least quarterly by the combined inter-disciplinary team (i.e. CF and diabetes teams). Some people may require more frequent review after initial diagnosis or if their clinical condition changes [615]. Aim to review trends in daily blood glucose levels at every appointment and to monitor HbA1c every 3 months to help guide insulin therapy decisions [238,619]. Routine measurement of weight, body mass index, lung function, bone mineral density and vitamin status should also occur [2,3].

HbA1c reflects average glycaemia over the preceding 6–8 weeks. [632]. In most people with CF-related diabetes, HbA1c treatment goal is <7% or 53 mmol/mol (although diabetes targets for type 1 diabetes have recently lowered to 6.5% or 48mmol/mol in the UK) to reduce risk of vascular complications [615,641,642]. However, an individualised approach is encouraged.

Further research into CF-related diabetes management may alter HbA1c and /or BGL targets however until then individualised targets should be balanced with overall health status.

Refer to chapter 16 for discussion of diabetes treatment targets are lung transplant.

SCREENING FOR COMPLICATIONS

Whilst macrovascular complications are rarely reported in people with CF-related diabetes, microvascular complications such as retinopathy, neuropathy and nephropathy can develop [643]. Available data suggest that complications are rare within the first five years of the onset of CF-related diabetes but, may become more common as individuals with CF- related diabetes progress into the fifth and sixth decades of life.

Accordingly, screening plays a crucial role in the identification of diabetic complications and is therefore strongly recommended [146,238,619]. The following tests should be undertaken:

- **Hypertension** - measurement of blood pressure is recommended at every diabetes clinic review [238].
- **Lipids** - complete lipid profiles are recommended annually, and are of particular significance for people with CF who are pancreatic sufficient, obese, or have a family history of cardiovascular disease or prescribed immunosuppressive therapy following transplant [238].
- **Neuropathy** - neurologic assessment and foot evaluation are recommended annually. Gastroparesis is common in CF patients and may make good glycaemic control difficult to achieve.

Every 5 years (after initial diagnosis) of CF-related diabetes, the following should be screened:

- **Retinopathy** - by ophthalmic assessment with dilated retinal examination [146].
- **Nephropathy** - via urinalysis [146]. Tight glycaemic control and treatment of microalbuminuria with ACE inhibitors or angiotensin receptor blockers combined with optimal control of hypertension, delay progression of diabetic renal disease in the general diabetes population [615]. They are assumed to also be beneficial for the relevant CF population although there are no specific data in this population.

CHAPTER 13 BONE HEALTH

N. Saxby, A. Kench & J Grunert

Building strong and healthy bones from childhood helps people with cystic fibrosis (CF) live active and independent lives. For people with CF, completing simple preventative measures such as getting enough vitamin D and calcium, and exercising regularly are known to positively affect bone health [78]. Health practitioners also play an important role in recognising CF-related bone disease early and intervening promptly [644]. Prompt intervention can optimise bone mineral accretion during childhood and adolescence and minimise bone losses in adulthood [644].

Disease Aetiology

Chronic illness and low bone mineral density can result in pubertal delay; in turn, low bone mineral density can be associated with osteoporotic or minimal impact-fractures in people with CF [644]. Fractures such as those in vertebrae and/or ribs can impair sputum clearance, pulmonary function, quality of life and working capacity [78,645]. Reduced bone accretion and accelerated bone loss are thought to contribute to reduced bone mineral density [644]. Causes of suboptimal bone health are complex and multifactorial. The following should be considered:

NUTRITION

- Undernutrition [230,646-649]
- Low lean body mass [262,646]
- Micronutrient deficiencies [78,650]

  Calcium Chapter 9
  - An important component of bone infrastructure [650]
  - Deficiency may result in bone calcium mobilisation to maintain serum calcium (calcium homeostasis)

  Vitamin D Chapter 8
  - Helps with calcium absorption

  Vitamin K Chapter 8
  - Necessary for posttranslational activation of osteocalcin, which in turn is important for bone formation and mineralisation
- Essential fatty acid deficiency Chapter 7 [651,652]

MEDICATIONS

- Corticosteroid use – oral, inhaled and nebulised [230,445,646,647,649,653,654]
  - Commonly used in the management of allergic bronchopulmonary aspergillosis (ABPA)
  - High doses may cause functional hypogonadotropic hypogonadism in both males and females [655]

CF GENOTYPE & COMORBIDITIES

- Complications of CF such as pancreatic insufficiency, CF-related diabetes, and chronic liver disease [644]
- Ongoing effect of inflammation caused by CF lung disease and pulmonary exacerbations, and advanced lung disease [646,656]
- CFTR gene
  - Contributes to reduced bone mineral density, via defective osteoblast maturation [657,658]
  - Particular link with Delta F508 genotype [262]

PUBERTY

- Pubertal delay may cause osteoporosis [222,646,649,659]

OTHER described risk factors/correlates

- Sex (gonadal) hormone deficiency [644]

- Sub optimal levels of exercise and physical activity – both cardiovascular and weight bearing [648,653,656,660]
- Male gender [262]
- Lung transplant (Chapter 16)
- Pregnancy and lactation [661]
    - Pregnancy can place additional stresses on the skeletal system. However this does not normally result in fractures or persistent osteoporosis
    - Prolonged breast feeding is associated with increased risk of osteoporosis at menopause in the general population

MEDICAL DIAGNOSTIC CRITERIA

The World Health Organization diagnostic criteria of bone mineral densities in adults are listed below (Table 13a) [662,663].

T-SCORES

- Represents the number of standard deviations of an individual's bone density in comparison to the peak bone density of healthy young adults of the same sex (i.e. at 30 years of age) [662,663].
- Not used in children and adolescents as peak bone mass has not been reached.

Z-SCORES

- Represents the number of standard deviations above or below what is normally expected from a child/adolescent of the same age, sex and ethnicity.
- Low bone mineral density is classified as a z-score ≤ -2 [149].
- In children and adolescents of short stature, use of height or stature age z-score adjustments will help avoid over-estimating deficits in bone mineral density [149]

Table 13a. Diagnostic criteria of bone mineral densities in adults [662,663]

Category	t-score
Normal bone density	>-1
Osteopaenia	-2.49 to ≤-1
Osteoporosis	≤ -2.5

Prevalence of CF-related bone disease is known to increase with age [644,645]. A systematic review found that less than 5 percent of children with CF have bone disease, however prevalence increases to around 20 percent in adolescence and up to 65 percent in adults aged 45 years and over [645].

Assessment

DIET

Review dietary intake with particular focus on the adequacy of dietary calcium, vitamin D and vitamin K sources. Additional points to consider during the dietary assessment:

- Intake of calcium, vitamin D and vitamin K from oral and/or enteral nutrition support
- Dietary quality

Recent studies in the general population show that a more nutrient dense dietary pattern is associated with higher bone mineral density [664,665].

Consider additional sources of calcium, vitamin D and vitamin K including the following:

- Prescribed supplements
- Over the counter preparations

CLINICAL

GENERAL CONSIDERATIONS

Review an individual's lung function (FEV_1 and FVC) and nutritional status

- Low bone mineral density is correlated with lower lung function and suboptimal nutritional status [646,647,656,660,666].
- Sup-optimal nutrition exerts its effects through potential delayed pubertal progression [666].

Monitor pubertal progression

- Measuring height and Tanner stage every six months in children and adolescents.
  - Tanner pubertal staging information can be found on current Australian growth charts. Available through the Australian Paediatric Endocrine Group.
- If height velocity is compromised, bone age should be assessed to look for evidence of constitutional delay
- If growth is poor (both weight and height percentiles) or if there is no progression of Tanner staging, a referral should be made to a paediatric endocrinologist.
  - Aiming for early intervention to optimise final height and bone density

Explore the use of anabolic steroids, which may be used by adolescent and young adult males who are trying to increase muscle mass [667].

- Anabolic steroids suppress testosterone levels. Adverse effects on bone density may occur if prolonged androgen suppression occurs following cessation of anabolic steroids [667].
- Testosterone is an anabolic steroid which can have positive effects on bone mineral density but should only be used under the supervision of an endocrinologist [650].

Consider CFTR modulators

- Therapeutic options which are targeted at correcting the underlying cellular defect in CF (e.g. CFTR modulator C18) show promise as future therapies for CF-related bone disease [644].

BONE MINERAL DENSITY SCREENING

How and when should bone mineral content and density be assessed for people with CF? PICO 13.1.1

[Ungraded] Insufficient evidence to make a recommendation specific to CF. Health professionals should follow consensus document recommendations for assessing bone mineral density for people with CF. [149]

The only evidence to guide practice for the assessment of bone health in CF comes from consensus based guidelines and recommendations. From 8 years of age, there should be proactive monitoring of bone mineral density. If reduced bone density is identified, treatment intervention should be considered [1,149,391]. Frequency of follow-up scanning is dependent on previous bone mineral density results, type of treatment that was initiated to improve bone mineral density and the emergency of additional risk factors of bone disease. When clinical status is stable, follow up scanning should be conducted at least:

- Every three to five years if bone mineral density was normal; z or T-scores > -1
- Every two years if bone mineral density was moderately reduced; z-score between –1 and –2; or T-score between –1 and –2.5
- Annually if bone mineral density was severely reduced; z-score <-2 or T-score <-2.5.

More frequent scanning is suggested if significant new risk factors emerge (e.g. prolonged corticosteroid exposure) [1,149,391]. The current gold standard for measuring bone mineral densities is dual energy X-ray absorptiometry (DEXA) [1,149,391]. These recommendations are in line with the 2006 version of this guideline[1]. There is no significant new evidence.

Additional points of interest regarding DEXA scans:

- Unnecessary to conduct bone mineral density screening in children less than eight years [1].
  - Low prevalence of CF-related bone disease in children
  - Lack of meaningful normative data
- In adults, measurements are to be taken of the lumbar spine and femoral neck with or without the forearm. In children, the usual measurement sites are the lumbar spine and whole body.
- Monitoring and management decisions are usually based on the site with the lowest bone mineral density [1].
  - It may be appropriate to use a weight adjusted density rather than age adjusted one, particularly where pubertal delay is present.

BIOCHEMICAL AND LABORATORY DATA

Annual assessment of key biochemical markers is recommended. Additional information regarding vitamin D and K testing can be found in Chapter 8.

VITAMIN D

Is there an ideal serum 25-hydroxyvitamin D level to aim for in people with CF? PICO 13.1.2

[Ungraded] Insufficient evidence specific to CF for the ideal serum 25-hydroxyvitamin D level. It is suggested that the general Australian and New Zealand goal of ≥50 nmol/L be used with a caveat for the time of year at which testing occurs.

Given the lack of any available evidence in the CF literature or otherwise showing improved clinical outcomes in bone health with an increased target of 75nmol/L, it is suggested that the general Australasian goal of ≥50 nmol/L be used. In addition, consider the impact of season on monitoring and measurement of vitamin D.

- Aim to measure 25-hydroxyvitamin D at the end of winter months or in early spring [668]
- If end of winter testing is not feasible, it has been suggested to aim for 10 to 20 nmol/L [668] above the range of ≥50nmol /L to allow for the seasonal decrease in winter (i.e. ≥60-70nmol/L)

Discuss any change in serum 25-hydroxyvitamin D targets and higher dose vitamin D supplementation with an endocrinologist. Long term outcomes have not been extensively studied in CF population, particularly in children and adolescents.

VITAMIN K

Serum vitamin K levels are unreliable and should not be used to assess vitamin K status in CF [202,408,411]. PIVKA-II (protein induced vitamin K absence-II) and uc-OC (undercarboxylated osteocalcin) are considered the most accurate measures of vitamin K status [365,408]. Measures of coagulation are typically used as surrogate measures of vitamin K status, but are not ideal. See Chapter 8 for additional information.

Intervention

Optimal bone health and management is best achieved by utilising the full expertise of the interdisciplinary CF team. In particular, the following members should be engaged and liaise with the endocrinologist as required:

- Respiratory physician
- Dietitian
- Physiotherapist
- Pharmacist

PREVENTION

Throughout the whole of the lifespan promote:

- Optimisation of nutritional status and growth
- A varied diet sufficient in energy, balanced in fatty acids, and high in sources of calcium, vitamin D and vitamin K;
  - Adequate calcium, vitamin D and K intake is especially important pre and during pubertal growth spurts
  - Vitamin D and K should be proactively supplemented for all patients with pancreatic insufficiency Chapter 8
- Good adherence with routinely prescribed vitamin and mineral supplements
- Ongoing exercise inclusive of weight bearing physical activity [669,670]
- Safe sun exposure

NUTRITION SUPPORT

What are the calcium requirements in CF to reduce the risk of low bone mineral density? PICO 13.1.3

[Grade D] Calcium requirements to reduce the risk of low bone mineral density in CF are unknown. At this time, health professionals should aim for the RDI when making calcium recommendations in CF. [150]

The RDI[4*] for calcium in the general population is outlined in Table 13b. Additional information regarding the RDI for calcium can be found via the Nutrient Reference Values for Australia & New Zealand webpage - *http://www.nrv.gov.au/.*

Table 13b. RDI of Calcium for People in Australia and New Zealand*.

Age	Males (mg/day)	Females (mg/day)
1 to 3 years	360	500
4 to 8 years	520	700
9 to 11 years	800	1000
12 to 13 years	1050	1300
14 to 18 years	1050	1300
19 to 30 years	840	1000
31 to 50 years	840	1000
51 to 70 years	840	1000
> 70 years	1100	1300

**Adapted from: National Health Medical Research Council and Ministry of Health New Zealand. Nutrient Reference Values for Australia and New Zealand (2006). Available at: http://www.nrv.gov.au/*

CONFIRMED OSTEOPAENIA OR OSTEOPOROSIS

Aim to achieve normal weight gain and growth in children and optimal weight in adults

- Nutrition support interventions may be required

Aim to supplement calcium and vitamin D

- Supplementation is recommended as first line treatment [442]

Does supplementing calcium above the RDI improve bone mineral density in CF? PICO 13.1.4

[Grade D] There is insufficient evidence to support that routine calcium supplementation above the RDI will improve bone mineral density in CF. Consider calcium supplementation only when dietary intake is unable to meet the RDI. [151]

In the absence of data specific to cystic fibrosis, the following consensus statements should be referred to:

- 2005 US Consensus statement: Guide to Bone Health and Disease in Cystic Fibrosis [391]
- 2011 European Cystic Fibrosis Bone Mineralisation Guidelines [149]

4 * RDI = the average amount of nutrient needed each day to meet the requirements of nearly all individuals.

Both recommend that calcium supplementation should follow country specific dietary reference intake (RDI) values. This is in line with a review of the evidence in the general population whereby calcium supplementation above the recommended level is unlikely to achieve additional benefit for bone health [671].

The Australian and New Zealand RDIs for calcium were determined by estimating accumulation of whole body calcium and converting this to a daily rate of calcium accretion [43]. Excessive supplementation of calcium above this level could lead to complications including hypercalcaemia, hypercalcuria, nephrolithiasis, constipation, vascular and soft tissue calcification, interactions with zinc and iron, and prostate cancer [439].

MEDICAL SUPPORT

Consider pubertal status:

- regular monitoring and review is encouraged
- check gonadal hormone levels and gondatropins in those with evidence of pubertal delay or reduced bone mineral density

Anti-bone resorptive medication (e.g. bisphosphonate treatments) are not routinely recommended for the CF population.

- Some evidence to show a potential benefit in CF whereby alendronate or zoledronate therapy can significantly improve bone mineral density in people with CF [442,672]
- There is no bone mineral density T-score or bone mineral density fall rate to indicate when bisphosphonate therapies should be considered. Australian prescribing criteria recommend zoledronate/alendronate or residronate therapy where:
    - Oral prednisone >7.5mg daily is used for >3 months and T scores show osteopaenia OR
    - There is a previous fracture with osteopaenic T scores (T-Score <-1.5)

Potential side effects of bisphosphonate treatments include hypocalcaemia, gastrointestinal irritation or ulceration, and musculoskeletal pain. Flu-like symptoms and injection site reactions may occur.

Hormonal therapy may be required with persistent hypogonadism or if there is pubertal delay which impacts an adolescent's interactions with their peers. Gonadal hormonal therapy remains controversial, thus endocrinologist supervision is essential [391,650]

- Hypogonadism can be a consequence of malnutrition, low body weight or supra-physiological doses of glucocorticoid resulting in hypothalamic – pituitary – gonadal axis suppression.
- Females who have hypothalamic suppression may require oestrogen hormonal therapy
- Gonadal steroids will not be effective if nutrition remains sub-optimal (evidence for eating disorder literature)

Due to the sensitive nature of this topic, it is important to involve both the adolescent with CF and their parents in discussions about potential use of hormonal therapy.

PHYSIOTHERAPY SUPPORT

Continue to promote exercise, including weight bearing physical activity, as this helps in maintaining bone mass and optimises lung health [669,670].

Monitoring & Evaluation

Bone health status should be periodically assessed and re-assessed in individuals with CF who are over eight years old. Ongoing interdisciplinary input is essential.

Practice Points PICO 13.1.1

2006 Australasian Clinical Practice Guidelines for Nutrition in CF: Assess bone mineral density periodically in people with CF who are more than eight years of age[1]. Dual energy X-ray absorptiometry scanning is the current gold standard assessment tool.

Follow up: Frequency of follow-up scanning is dependent on previous bone mineral density results, type of treatment that was initiated to improve bone mineral density and the emergency of additional risk factors of bone disease. When clinical status is stable, follow-up scanning should be conducted at least:

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

More frequent DEXA scanning is suggested if significant new risk factors emerge (e.g. prolonged corticosteroid exposure)

Practice Points PICO 13.1.2

It is suggested that the general Australasian goal of ≥50 nmol/L serum 25(OH)D be used if measuring vitamin D at the end of winter or in early spring. If testing at other times of year, aim for a level 10-20nmol/L higher (≥60-70nmol/L).

Practice Points PICO 13.1.3 and 13.1.4

Foods high in calcium include dairy foods (e.g. cow's milk, cheese & yoghurt), fortified dairy alternatives (i.e. soy milk), firm tofu & bony fish. Legumes, nuts and some green vegetables also contain small amounts of calcium. More information regarding the RDI for calcium can be found via the Nutrient Reference Values for Australia & New Zealand webpage - *http://www.nrv.gov.au/*

CHAPTER 14 SPECIAL CONSIDERATIONS FOR LIFE STAGE AND GENOTYPE

K. Herd, C. Painter, N. Saxby, T. Crowder, A. Matson & J. Stonestreet

This section covers the nutritional implications of pregnancy and genetic modulator therapies.

14.1 Pregnancy

K. Herd, T. Crowder & A. Matson

Pregnancy in women with CF is increasingly common. In Australia, approximately one in seven adults with CF have had children (majority: fathers) [673]. Most adult CF centres will need to provide pre-natal and post-partum care.

Many pregnancies in women with CF have been reported in the literature, generally with very good outcomes for both mother and baby, although some women do experience difficulties including maintaining adequate nutrition and an unpredictable effect on lung function [674]. Every pregnancy in CF should be considered as potentially high risk for both the mother and the foetus due to the effect on lung function [675]. The role that maternal nutrition plays prior to conception and throughout pregnancy is extremely important. Positive outcomes for both the woman with CF and her infant are associated with better nutritional status. Before pregnancy, a BMI greater or equal to 22kg/m^2 is recommended [633,676].

Assessment

A comprehensive nutrition assessment prior to conception provides an opportunity to optimise the nutritional status of a woman with CF. When the pregnancy is unplanned prompt nutrition assessment and counselling is essential. Ongoing nutrition assessments during the pregnancy and post-partum are also essential [677].

DIET

Review diet history including a quantitative assessment of dietary intake and an assessment of vitamin and mineral supplementation, enzymes, oral and enteral nutrition support to address the requirements of pregnancy combined with CF.

CLINICAL

Key points to consider as part of a clinical nutrition assessment include:

- Anthropometry – including weight history prior to and during pregnancy
- Factors that may affect dietary intake:
    - nausea, vomiting, reflux and constipation
    - increased shortness of breath and coughing may become more frequent in the 3rd trimester
- Respiratory function tests and history prior to and during pregnancy

SCREENING FOR GESTATIONAL DIABETES MELLITUS

Pregnant women with CF should be screened for gestational diabetes mellitus. The following is recommended:

- A 2hr 75g fasting OGTT is recommended for any woman with CF who is planning a pregnancy or is confirmed pregnant if there has not been a normal CF-related diabetes screen in the last 6 months
- A 2hr 75g fasting OGTT with blood glucose measures at 0, 1, and 2 hours is also recommended at both 12–16wk and 24–28wk gestation in pregnant women with CF not known to have CF-related diabetes
- Post-pregnancy screening for CF-related diabetes using a 2-h 75g fasting OGTT is recommended 6–12wk post-partum[146]

People with CF may be diagnosed with gestational diabetes mellitus (GDM) based on recommendations of HAPO Study Cooperative Research 2008 [624] and the Australasian Diabetes in Pregnancy Society [625] (see table 14a).

Table 14a. Recommendations for diagnosis of gestational diabetes mellitus in people with CF

Gestational diabetes mellitus diagnosis	Blood glucose levels
Fasting plasma glucose (FPG)	>5.1mmol/l / (92mg/dL)
OR 1 hour plasma glucose	> 10 mmol/l / (180mg/dL)
OR 2 hour plasma glucose	>8.5 mmol/l / (153 mg/dl)

People with CF and diagnosed gestational diabetes mellitus are not considered to have CF-related diabetes. However, they do require screening for CF-related diabetes 6-12weeks post-partum. The 2hr 75g fasting OGTT is again recommended [146,624,625].

BIOCHEMICAL AND LABORATORY DATA

The following laboratory data should be collected [633]:

- Serum vitamin A
  - prior to conception or at the onset of pregnancy and at the beginning of the second and third trimesters
- Serum vitamin D
  - prior to conception or at the onset of pregnancy and/or at the beginning of the second and third trimesters
- Serum vitamin E
  - prior to conception or at the onset of pregnancy
- Iron studies at 20 weeks and supplementation considered if deficiency is developing

Chapter 8 and Chapter 9 respectively, provide further information on fat soluble vitamins and minerals.

Intervention

What are the nutrition considerations of the management of pregnancy in CF? PICO 14.1.1

[Ungraded] There is insufficient evidence to make a CF-specific recommendation.

Practitioners should be guided by the most recent guidelines for pregnancy and CF [633].

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 (eg. listeriosis, toxoplasmosis and salmonellosis) and mercury poisoning from fish, which are potentially harmful to the foetus. Furthermore, information should be provided on alcohol, caffeine and fish consumption akin to that for the general population [152].

FOLIC ACID

The role of folic acid in pregnancy is well established in the literature for the general population. However, recommendations for supplementation vary between countries. Factors specific to CF have not been identified.

Australian recommendations (general population):

- All women planning a pregnancy should take a daily supplement of 0.4mg folic acid per day per day pre-conception and in the first trimester to prevent neural tube defects [678].

New Zealand recommendations (general population):

- All women should take 0.8mg folic acid per day pre conception and in the first trimester [153].
- Women with risk factors such as family history of neural tube defects, taking certain medications or having insulin dependent diabetes should be considered for additional supplementation of 5mg folic acid per day [153].

VITAMIN A

What recommendations around vitamin A supplementation and monitoring should be provided to women with CF who are pregnant or planning a pregnancy PICO 14.1.2

[Ungraded] There is insufficient evidence to make a CF-specific recommendation.

Both vitamin A deficiency and excess are teratogenic and associated with adverse reproductive outcomes [675,677]. Assessment of vitamin A intake and status should be undertaken in the pre-conception period to establish that levels are within the normal range. Particular attention should be given to preformed vitamin A (i.e. retinol). Unlike preformed vitamin A, beta-carotene is not known to be teratogenic [302]. The total retinol equivalent (RE) intake, which will include the preformed and provitamin A intake, and the contribution of beta-carotene, should be adjusted based on serum retinol levels, with the goal of maintaining serum levels within the normal reference range. If serum vitamin A levels are normal, supplementation should continue at a dose <10,000 IU/day [411,633]. If levels are high it is considered prudent that the level of vitamin A supplementation is reduced [279,285] . Supplementation above upper recommended limits should only be recommended with caution. For people with CF are pancreatic insufficient and pregnant, vitamin A supplementation is still required in most circumstances. It is not currently recommended to cease all vitamin A supplementation in pregnancy and monitoring of its need is important. It is essential to review all non-prescription, over the counter and herbal vitamins/products that women may be taking. Chapter 8 provides further information regarding supplementation, assessment and monitoring of vitamin A.

OTHER CONSIDERATIONS

Due to increased requirements in pregnancy, both the Australian and New Zealand health bodies recommend that all women who are pregnant or considering pregnancy, take an iodine supplement of 150 micrograms (µg) each day [152,153].

The recommended dietary intake (RDI) for iron in pregnancy is 27mg/day and when lactating 9mg/day [43]. For this reason, iron supplementation may also be required for women with CF diagnosed with an iron deficiency during their pregnancy. The RDI for calcium in both the pregnant and lactating woman is 1000mg/day, unchanged from the RDI for adult females [43]. Chapter 9 discusses assessing, monitoring and supplementation of minerals in greater detail. Vitamins D and E should continue to be monitored and supplemented to maintain levels in the recommended reference range. See Chapter 8 for further information

WEIGHT AND NUTRITION STATUS PRE CONCEPTION, DURING PREGNANCY AND POST PREGNANCY

An overall weight gain of 12.5kg is considered typical for pregnancy and a weight gain of at least 11 kg has been recommended for women with CF [679]. It may be useful to set a goal weight for each trimester to ensure overall weight targets are achieved. The recommended energy requirements for pregnancy vary from an extra 800-1200kJ/day per day. Women with CF, poor nutrition and low BMI prior to conception may need even more energy [674]. Women with inadequately malabsorption control due to pancreatic insufficiency, and increased energy loss may require even greater energy intake to support adequate weight gain for pregnancy.

For women with or without CF, preconception weight, rate of weight gain during pregnancy, and total weight gain are crucial for both the health of the baby and the woman postpartum. Both the Australian and New Zealand governments have recommendations for total weight gain based on pre-pregnancy BMI, see Table 14b below [152,680]. Although not specific to CF this is useful to guide practice.

Table 14b. Recommendations for total weight gain during pregnancy, by pre-pregnancy or early pregnancy (less than 10 weeks) BMI

Pre-pregnancy or early pregnancy (<10 weeks)	Total weight gain
BMI <18.5 Kg/m2	12.5 – 18 Kg
BMI 18.5 – 24.9 Kg/m2	11.5 – 16 Kg
BMI 25.0-29.9 Kg/m2	7 – 11.5 Kg
BMI ≥ 30 Kg/m2	5 – 9 Kg

In order to achieve an optimal nutritional status prior to pregnancy and/or adequate weight gain during pregnancy, dietary intake and absorption should be maximized. If nutritional status cannot be optimised by a high energy diet alone, oral nutrition supplements or enteral nutrition support should be considered [681]. In those requiring tube feeding for the first time; it is best considered early in pregnancy when best tolerated. See to Chapter 6 for further information.

GESTATIONAL DIABETES

CF-specific blood glucose targets for the woman with gestational diabetes have not been established. Recommendations from the American Diabetes Association [146] for women with gestational diabetes should be followed. These targets are recorded in table 14c.

WOMEN WITH EXISTING CF-RELATED DIABETES

Women with established CF-related diabetes, who are planning a pregnancy or who are already pregnant, should optimise glucose control by adjusting their insulin regimen according to review by specialist endocrine and obstetric teams [633]. The Australasian Diabetes in Pregnancy Society (ADIPS) has recommended BGL targets at fasting, one and two hours post prandial, as follows [625]:

Table 14c. Targets for blood glucose levels in pregnancy for CF-related diabetes and gestational diabetes mellitus

	CF-related diabetes in pregnancy	Gestational diabetes mellitus
Fasting	5.0	5.3
1-hr postprandial	7.2 – 7.8	7.8
2-hr postprandial	6.7	6.7
A1C	6.0-6.5% recommended <6.0% may be optimal as pregnancy progresses	

BREASTFEEDING

The mother's choice of infant feeding method should be supported and it is prudent to discuss options during pregnancy. Many women with CF will be motivated to try to establish breastfeeding. Breast feeding in the mother with CF can be successfully undertaken, however close monitoring of nutritional status and fatigue should be undertaken [633]. Breastfeeding further increases maternal energy, nutrient and fluid requirements and it can also be challenging for the mother to perform her regular treatment whilst looking after a newborn [675]. It is important to support the mother in order to achieve optimal health for both herself and her newborn. Some women with CF will successfully maintain adequate health and nutritional status whilst breastfeeding with support from their healthcare team and family supports.

Monitoring & Evaluation

Aim to monitor the following closely:

- Weight gain
- Hydration status
- Development and/or management of gestational diabetes

Excellent communication between the CF specialist team and the obstetric service is required to ensure the best outcome for both the mother and infant [675].

Practice Points PICO 14.1.1

- Before pregnancy a BMI greater or equal to 22kg/m^2 is recommended.
- Undertake a comprehensive nutrition assessment prior to conception and ongoing during pregnancy and post-partum, including standard pregnancy counselling around food safety, alcohol, caffeine and fish consumption recommendations as per Australian [152] and NZ recommendations [153].
- Clinicians should be guided by local country recommendations for supplementation amounts of folic acid. Assess the need for additional supplementation of 5mg folic acid per day in women with risk factors such as family history of neural tube defects, taking certain medications or with insulin dependent diabetes.
- Screening for Gestational Diabetes Mellitus is recommended via a 2hr 75g fasting OGTT when pregnancy is confirmed, at 12-16 weeks and 24-28 weeks gestation. Screen for CF-related diabetes at 6-12 weeks post-partum.
- Measure levels of fat soluble vitamins A, D and E at first review after pregnancy confirmation and the beginning of the second and third trimesters. Monitor levels and supplement to maintain in the reference range (refer to PP 14.2 for specific information about vitamin A supplementation).
- Undertake iron studies at 20 weeks' gestation and assess the need for supplementation if deficiency is developing. Tolerance of supplementation can be problematic in pregnancy further aggravating gastrointestinal symptoms especially constipation. Preventative management strategies including use of stool softening agents can be helpful.
- Weight gain of at least 11 kg has been recommended for women with CF. If nutritional status cannot be optimised by a high energy diet alone, explore oral nutrition supplements or enteral nutrition support. In those requiring tube feeding for the first time; it is best commenced early in pregnancy when best tolerated
- It is important to discuss infant feeding options during pregnancy with women with CF. Breast feeding in the mother with CF can be successfully undertaken, however close monitoring of nutritional status and fatigue should be undertaken
- It is important to monitor the weight of the woman with CF post-partum. Significant weight loss due to breastfeeding, and potential time burden that may compromise self-care can impact on overall health. Optimising nutrition at this time is vital.
- For any complex issues in the pregnant woman with CF, consult a CF specialist adult centre.

Practice Points PICO 14.1.2

- Measure fat soluble vitamin A level at first review after pregnancy confirmation and at the beginning of the second and third trimesters.
- If normal vitamin A levels, supplementation should continue at a dose <10,000 IU/day of retinol. These levels are in line with recommendations for the healthy population in pregnancy.
- Reassure the woman that supplements are being prescribed to prevent vitamin A deficiency which like vitamin A excess, is also teratogenic.
- If vitamin A levels are high, it is recommended to reduce vitamin A supplementation. A different multivitamin supplement may be required with lower vitamin A (particularly preformed vitamin A, retinol). Assess adequacy of other fat soluble vitamins if the CF-specific multivitamin is ceased.
- More frequent monitoring of vitamin A levels may be required following changes to supplement formulation and/or dose.
- Review dietary intake of vitamin A including oral and enteral supplements with particular attention to high retinol sources.
- Review all non-prescription, over the counter supplements with particular consideration for high retinol supplements (e.g. cod liver oil).

Translating into Practice

- The common multivitamin preparation used in CF management vitABDECK contains 0.4mg folic acid, but nil iodine. Iodine is available in other multivitamin preparations or through a folic acid and iodine combination supplement.
- VitABDECK contains Vitamin A as preformed retinol 2500IU and beta-carotene 3mg (1665IU). People with CF who are pregnant and taking vitABDECK prior to pregnancy should continue use unless alternate management is recommended by CF healthcare provider following thorough assessment.
- Iron supplementation can be problematic in pregnancy further aggravating gastrointestinal symptoms especially constipation. Preventative management strategies including use of stool softening agents can be helpful. A review of salt, fluid and fibre intake may also be beneficial.
- It is important to monitor the weight of the woman with CF post-partum. Significant weight loss due to limited time and self- care can impact overall health and optimizing nutrition at this time is vital.
- Breastfeeding mothers require close monitoring to ensure maintenance of adequate nutritional status

14.2 Genetic modulator therapies

C. Painter, N. Saxby & J. Stonestreet

CF is caused by over 1700 different mutations in the CFTR gene, which are classified into six different classes based on the protein defect that causes disease [682,683], as shown in table 14d below. Recent advancements in therapies target correction of the function of this underlying defective protein. These treatments are called genetic modulators [684]. Gene modulators are targeted towards specific gene mutations, and are categorized into two groups: CFTR potentiators and CFTR correctors.

Genetic modulator therapy is an emerging field, and so it is important to note that the information provided in this section reflects the publication date.

Table 14d. Classifications of Gene Mutations That Cause Cystic Fibrosis*

Class	Example mutations	Description
I	G542X, R1162X W1282X	Mutations impair protein production, and being often nonsense mutations (with premature stop condons) they lead to mRNA degradation by a process called nonsense-medicated decay.
II	F508del R560T A561E	Affect CFTR processing due to misfolding which is recognized by endoplasmic reticulum quality control retention and which targets proteins with abnormal conformations to degradation.
III	G551D	Disrupt CFTR channel regulation through impaired gating.
IV	R334W	Decrease chloride ion conductance (flow) through chloride channel.
V	3272-26A>G	Significantly reduce normal protein levels, often by affecting splicing and generating both aberrant and normal transcripts
VI	F508del after rescuing to cell surface	Lead to decreased retention/anchoring at the cell surface, often associated with decreased protein stability at the plasma membrane

*Adapted from Bell, et al. [683]

IVACAFTOR

Ivacaftor (also known as VX-770 and Kalydeco®) is a CFTR potentiator which improves CFTR protein function at the epithelial cell surface [684]. Due to its mechanism of action, Ivacaftor is only suitable for people with class III and IV CFTR mutations (e.g. G551D, G1244E, G1349D, G178R, G551S, S1251M. S1255P, S549N, S549R and R117H) [684]. Ivacaftor has been proven safe and efficacious in people aged six years and over [155,158]. A recently published study by Davies et al also demonstrated the safety of Ivacaftor for children ages two to five years over a period of 24 weeks [530]. Longer follow up trials are yet to be completed.

In Australia approximately 300 people, aged six years or more with one of the nine specified gating mutations, are eligible to be prescribed subsidised Ivacaftor through the Pharmaceutical Benefits Scheme (PBS)[685,686]. Although Ivacaftor is approved in the United States of America for people with CF over the age of six who have one R117H mutation, this does not extend to Australia. The New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE) have also approved the safety of Ivacaftor but funding is yet to be addressed.

Significant improvements in respiratory, nutritional and quality of life outcomes have been documented for people receiving Ivacaftor [154-159,161,162,530], which may change the nutritional needs of people with CF.

Due to the molecular target of Ivacaftor, it is not suitable for more than 90 percent of the CF population based on their CFTR mutations. Research into targeted therapies for more common CF genotypes is a priority [684]. Phase III trials of the CFTR corrector/potentiator therapy Lumacaftor/Ivacaftor (also known as VX-809 and Orkambi®) for people who are homozygous F508del have shown minimal improvements in respiratory outcomes, hospitalization frequency and BMI [687]. Improvements observed with this medication offer minimal clinical advantage (i.e. lung function clinical benefit was much lower than that demonstrated by Ivacaftor and the gating mutations). Ongoing studies with an alternative CFTR corrector (VX-661) in combination with Ivacaftor continue in both F508del homozygous and heterozygous populations. Lumacaftor/Ivacaftor is approved in Australia for those people homogyzous for F508del alleles aged 12 years; however, this medication is not currently reimbursed by the government and thus it is not widely available. No CFTR corrector therapies are approved for use in New Zealand.

Whilst the success of these early CFTR modulators has dominated the literature in recent years, other gene specific therapies such as correctors and read-through-agents offer great promise for future therapeutic options [684].

Disease Aetiology

What are the implications of Ivacaftor on nutritional status in children >2 years and adults with cystic fibrosis who have at least one G551D or other gating mutation allele? PICO 14.2.1

[Grade A] There is evidence to suggest that continued use of Ivacaftor therapy leads to significant improvements in weight and BMI in adults and children > 2 years. [154-161]

Weight gain is likely to be multifactorial and is currently not well understood. The weight gain seen in adult populations is mostly within the first month and then plateaus [154,156,158], while paediatric patients continue to gain weight over time, as would be expected [155,157,158]. Due to the wide range of ages of children and adolescents collectively studied it is difficult to interpret weight gain patterns.

Whilst not included in the formation of the evidence-based recommendation above, an ongoing study shows that, in adults, acute weight gained after commencement of Ivacaftor reflects an increase in total body water [688]. Increase in fat free mass does not occur until 1 month after treatment. Further validation is underway.

Are there any other nutritional considerations (energy, salt intake) that practitioners should take into consideration for people on Ivacaftor therapy? PICO 14.2.2

[Grade D] Well-nourished individuals on Ivacaftor therapy may benefit from dietary advice consistent with the general healthy population recommendations, although at this stage there is insufficient evidence to recommend routine changes of energy and salt intake for people with CF receiving this medication. [154-163]

Significant improvements in sweat chloride levels are noted across studies [154,155,157,159,530]; however, the relationship between sodium intake and sweat chloride levels is currently unknown [156]. In 2015, McKay et al. demonstrated that the majority of patients receiving Ivacaftor therapy (approximately 80 percent) had substantially improved fat intake and decreased fat excretion [689].

Several factors contributing to improvements in nutritional outcomes post Ivacaftor have been hypothesised including gut pH increases (i.e. less acidic) and energy balance changes [690]. A recent publication has also shown that the histological changes of CF revert to normal after Ivacaftor use [691]. Changes in gut pH may have implications for the use of acid regulation medication which is often required concurrently with enzyme therapy to enhance enzyme activity and fat absorption (e.g. PPIs). In addition, one small pilot study of five individuals suggests that Ivacaftor

therapy may improve glucose tolerance [163]. Secondary analysis of Phase III randomized control trial data by Borowitz, et al. [692] revealed that there were no linear correlations between changes in body weight seen and improvements in FEV1 or chloride levels. A recent study also showed significant improvements in faecal elastase concentration (a measure of pancreatic function) after treatment with Ivacaftor, with some participants aged 2-5yo converting from abnormal to normal pancreatic function after 24 weeks of treatment [530].

Further research is required on the nutritional implications of Ivacaftor therapy, specifically its effects on body composition, bone mineral density, energy and salt requirements, enzyme dosing and acid regulation.

Assessment

What is role of gastrointestinal and/or other nutritional outcome measures in people with CF receiving Ivacaftor therapy? PICO 14.2.3

[Ungraded] There is insufficient evidence to make a CF-specific recommendation.

There is currently no specific evidence available to guide practice in this area. Nevertheless, practical considerations for the nutritional assessment of people on genetic potentiator therapy can be inferred from the available literature.

DIET

Complete a comprehensive dietary assessment, ensuring that genetic modulators are being taken per prescribed dosing recommendations, with a fat containing meal or snack (amount and type of fat are not important). Ensure appropriate enzyme dosing for the meal or snack.

CLINICAL

- People with CF-related diabetes on insulin are at risk of experiencing hypoglycemia, especially upon commencement of Ivacaftor – close monitoring of blood glucose levels may be appropriate [693]
- Regularly monitor weight gain and trends (including BMI) and consider body composition to prevent excessive increases in fat mass. Other accepted clinical endpoints to measure nutritional status such as body measurements and waist circumferences have limitations when used with the CF population as discussed in Chapter 5 Nutrition Assessment
- Monitor perception of body image.

BIOCHEMICAL AND LABORATORY DATA

A recent descriptive analysis reviewed the clinical relevance, reliability, validity, and feasibility of using gastrointestinal outcome measures to measure CFTR protein function [690]. To help guide concurrent nutritional related therapies (e.g. PERT and PPIs), practitioners may wish to examine faecal elastase and measure intestinal fat absorption for people with CF of all ages being treated with CFTR modulators [690].

Intervention

Working proactively with the person with CF and/or their family, consider discussing the following:

- discuss possible nutritional implications, weight, diet choices and the importance of individualised dietary adaptations
- the potential impact on PERT and sodium
- the potential impact of weight changes and any related concerns

Individuals with CF-related and/or CF-related liver disease may have additional nutrition related concerns (e.g. episodes hypoglycemia, raised liver function test results). These concerns should be reviewed in the context of the individual's CF disease and dietary intake, as well as potential side effect/s of CFTR modulator therapy [693].

Monitoring & Evaluation

Dietitians should aim to engage individuals with CF on CFTR modulator therapies every three months to ensure nutrition status, dietary management and weight gain are monitored proactively, ideally in conjunction / alongside the interdisciplinary team.

If the course of CF lung disease is altered (e.g. change in exacerbations frequency), an individual's nutritional status and/or dietary intake patterns may change if overall nutritional requirements reduce, or appetite and intake become less variable over time. Reduction in overall energy intake may not be a concern if adequate nutritional status is maintained; however attention to diet quality may be required.

Practice Points PICO 14.2.1 and 14.2.2

- Practitioners need to proactively monitor weight gain patterns throughout the first few years of Ivacaftor therapy so that nutritional recommendations can be tailored to the rapidly changing body composition.
- People with CF-related diabetes are at risk of experiencing hypoglycemia, especially upon commencement of Ivacaftor – monitor blood glucose levels closely
- The relationship between sodium intake and sweat chloride levels is currently unknown. There is not yet clear evidence for a change in salt supplementation requirements, but provide advice on sodium requirements based on the person's signs and symptoms of salt depletion.
- Genetic modulators should be taken with a fat containing meal or snack
  - People who are PI should also take their PERT at this time
- Children:
  - After establishment of Ivacaftor ensure that catch up growth is achieved before considering altering a child's diet in terms of energy and/or salt.
- If the course of CF lung disease is altered (e.g. a reduction in exacerbation frequency), an individual's nutritional status or dietary intake pattern may also change if overall nutritional requirements are lowered or appetite/intake becomes more stable. A reduction in overall energy intake may not be a concern if adequate nutritional status is maintained, however attention to diet quality may be required.

Practice Points PICO 14.2.3

Gastrointestinal outcome measures such as faecal elastase and intestinal fat absorption are appropriate to use in this population group. Use of these tests may help guide practitioners in what are appropriate concurrent nutritional therapies (i.e. PERT and protein pump inhibitors).

As genetic modulator therapies are relatively new, it is possible that a range of clinical and symptomatic observations will be made, about which more evidence to guide practice recommendations may emerge in the future in relation to modulation or restoration of physiological functions affected by CFTR. There is limited evidence to date of the impact of other CFTR modulator therapies on gastrointestinal function or nutritional outcome measures. Until such evidence is available, identify and evaluate any changes in gastrointestinal or other symptoms in people taking CFTR modulator therapies.

CHAPTER 15 COMPLEMENTARY NUTRITION THERAPIES

C. Miles, A. Tierney, J. Anderson & J. Heyward

Complementary therapies are defined as medicinal products containing active ingredients such as herbs, vitamins and minerals, nutritional supplements, homoeopathic medicines and aromatherapy products each of which have a clearly established identity and traditional use in medicine [694]. The use of complementary therapies in chronic disease has increased significantly over the last twenty years and is continuing to gain medical, economic and sociological importance [695]. Recent estimates suggest that up to 75 percent of children with CF [696,697] and up to 70 percent of adults with CF [698] have used complementary therapies in addition to conventional treatments.

Complementary therapies are regulated in Australia by the Therapeutic Goods Administration under the Therapeutic Goods Act 1989 [694] and in NZ by the Ministry of Health under the Natural Health and Supplementary Products Bill 2012 [699]. This chapter will discuss evidence for the use of probiotics, glutathione, coconut oil and herbal supplements in people with CF.

15.1 Probiotics

J. Anderson, A. Tierney & C. Miles

A diverse range of over 100 trillion microorganisms colonizes the human gastrointestinal tract. The composition of the microbiota is influenced by factors including age, disease and diet [700]. The gut microbiota profile of an individual (i.e. bacteria living within the gut) begins to develop as early as *in utero* and progresses rapidly in richness and diversity during the first twelve months of life and beyond. By the end of the first three years of life, the microbiota of healthy children converges toward the characteristic diverse adult microbiota profile [701-703]. The adult microbiota is more distinct and stable and whilst it may continue to change, it does so at a much slower rate than in early childhood [704]. It has been postulated that for permanent change to gut microbiota, alterations to the host's microbiome must occur within the first few months and years of life [705].

Gastrointestinal microbiota play an important role in health and disease. A well-balanced gut microbiota has been associated with good immune function, prevention of infection from pathogenic or opportunistic microbes, and metabolic homeostasis [706]. Disruption to healthy gut microbiota, known as dysbiosis, has been associated with a number of inflammatory conditions including inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) as well as respiratory conditions such as allergic airway inflammation [707]. Probiotic efficacy has also been shown in the treatment of antibiotic and *Clostridium difficile*-associated diarrhoea [703,708].

A person's native gut microbiota may not always be able to perform its immune and metabolic functions optimally and therefore modulation of the gut microbiota is being increasingly considered a viable therapeutic strategy. Modulation of the gut microbiota can be achieved through the administration of probiotic supplements [703].
Probiotics are defined by the World Health Organisation as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [709]. The mechanism and efficacy of probiotics are strain-specific [710]. General health effects of probiotics cannot be extrapolated from one strain to another strain, nor are all probiotics indicated for the same health conditions [703].

The most common bacterial genera marketed as probiotics are lactic bacteria, such as *Lactobacillus* and *Bifidobacterium* [703]. Due to their strain-specific effects, probiotics must be identified and characterised to the level of the phyla, genus, species and strain [709]. An example of this is outlined in figure 15a below.

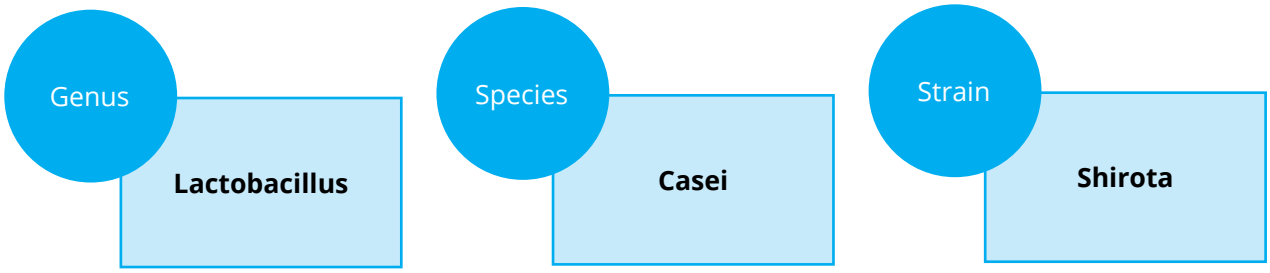

Figure 15a. Example of probiotic identification according to genus, species and strain.

Probiotics are now widely available to the general population and exist in many forms, including food and dietary supplements. Probiotic products vary considerably not only in their form, but in their intended health claim, quality, dose and storage requirements. In recent years, several clinically tested probiotic products have become available with quality-controlled production and are marketed by reputable companies, however, regulatory issues remain a challenge [708].

In Australia and New Zealand, probiotic products are considered as either functional foods, regulated by Food Standards Australia New Zealand (FSANZ), or complementary medicines, regulated by the Therapeutic Goods Administration (TGA) and New Zealand Ministry of Health. Under the Food Standards Code, fermented milk beverages and yoghurts that claim to be probiotic must have a minimum of one million live bacteria per gram. While complementary medicines must show the amount of an active ingredient, foods do not have to disclose the number of probiotic bacteria in a product, which can make it difficult for consumers to make an informed purchase. Of concern is the significant variability in product quality, purity and viability, with some products likely to have fewer probiotics than they claim [700,711].

Disease Aetiology

The gut microbiota in people with CF is thought to be different from those without CF. A state of dysbiosis has been demonstrated in the CF gut with an abundance of potentially pathogenic bacteria and a reduction in beneficial bacteria [236,712-714].

Gut microbiota profiles can be affected by numerous factors associated with CF including viscous mucus, intestinal dysmotility, reduced intestinal pH, reduced bile salt secretion, intestinal inflammation, chronic antibiotic and pancreatic enzyme use and bacterial overgrowth [236]. It is hypothesised that the intestinal mucosa in CF acts as the primary interface between the gut microbiota, immune and metabolic systems [712]. Abnormal intestinal mucosa is also likely to be associated with dysbiosis which may contribute to chronic pulmonary and intestinal inflammation and to the later development of gastrointestinal malignancies [712]. For these reasons, manipulation of the gut microbiota may have therapeutic potential in reducing chronic inflammation seen in CF [236].

The 'lung-gut axis' is a new area of research into the interconnectedness of pulmonary and gastrointestinal microbiomes [168,715]. It is suggested that gut microbiota in CF may be related to bacterial colonisation in the respiratory tract and the regulation of respiratory outcomes [712,716]. One proposed mechanism is by the action of T-cells, whereby alteration of the gut microbiota with probiotics improves respiratory disease via initiation of a T-cell regulatory mediated mechanism in the gut [716]. Chronic respiratory inflammation in CF may therefore benefit from strategies targeting the gut microbiota that influence the entire immune environment [716].

Does dietary supplementation with probiotic genus *Lactobacillus* improve nutritional and/or respiratory status in people with CF? PICO 15.1.1

[Grade C] Dietary supplementation with a *Lactobacillus* genus probiotic (single or as part of a mixture) may have health benefits for people with CF, particularly in regards to intestinal inflammation, the intestinal microbiota and risk of pulmonary exacerbation. [164-171]

The potential mechanisms of action by which probiotics may benefit individuals with CF include their effects on the gut microbiota, changes to gut motility, improved intestinal barrier function, inhibition of the colonisation of pathogenic bacteria, improved metabolic process and modulation of gut and systemic immunity [712,717].

Beneficial effects of probiotic supplementation have been demonstrated in CF, on a number of health outcomes, as outlined below [707]. However, it is important to note that the existing evidence is underpowered, of low quality and is inconsistent with regards to the health outcomes, population, probiotic strain and duration of supplementation examined. Care should be taken at this time when applying this evidence to clinical practice.

INTESTINAL INFLAMMATION

A reduction in intestinal inflammation (as measured indirectly by faecal calprotectin) has been demonstrated in people with CF, after supplementation with *Lactobacillus* as a single species/strain of probiotic [164,166,167,169] or as part of a probiotic mixture with a prebiotic [169].

INTESTINAL MICROBIOTA

Partial restoration of the normal intestinal microbial profile has been reported post probiotic supplementation in people with CF [164,167].

PULMONARY EXACERBATIONS

A reduction in the incidence and/or risk of pulmonary exacerbations has been shown in people with CF taking *Lactobacillus* probiotic supplements as a single strain/species [165,168,170,171].

Overall there were no beneficial effects of probiotics on FEV_1 [165,167,168,171]; inflammatory markers IL-8 and TNF-α [167,168,171]; or nutritional status as measured by BMI [165,167,171].

Assessment

DIET

Current or previous use of probiotics and their effects should be noted as part of a nutrition assessment. Probiotic intake may be from a supplement, in tablet, capsule or powder form and/or as a component in foods such as some yoghurts and fermented dairy drinks.

Many yoghurts contain live-active *Lactobacillus* cultures and are considered functional food products, however, most are not considered probiotics *per se*. The live cultures are added to milk to make yoghurt and are often called 'starter cultures'. A yoghurt therefore is not necessarily a probiotic unless it is fortified with an adequate number of viable bacteria shown to exert benefit in controlled trials [708].

CLINICAL

SAFETY CONSIDERATIONS

Definitive data on the safety of probiotics is limited. Species of *Lactobacilli* and *Bifidobacteria* are normal residents of, or common transients through, the human digestive system and as such do not display infectivity or toxicity [703]. These lactic bacteria are generally considered safe for oral consumption as part of foods and supplements for the generally healthy population and at levels traditionally used [703].

Overall there does not appear to be a risk in using probiotics however the reporting of side effects and adverse events in studies is generally poor. A large systematic review of probiotic safety in a range of population groups and a review in immune compromised adults, found no significant effect of probiotics on adverse events experienced [718,719]. However the literature is not well equipped to answer questions on the safety of probiotic interventions with confidence [718]. Until there is more robust evidence regarding the safety of probiotics in CF, they should continue to be used with caution in high risk patients such as those with severe lung disease [707]. Care should also be taken administering probiotics to those with venous catheters due to risk of sepsis [719].

Intervention

Should routine or targeted use of probiotic supplements be recommended for people with CF? PICO 15.1.2

[Grade C] The body of evidence to support health benefits from probiotic supplementation in CF is growing, however there is insufficient high quality evidence to support the *routine* or *targeted* supplementation of probiotics in individuals with CF. [164-171]

There is insufficient evidence at this time to recommend any specific probiotic species and strain, dose or frequency, as being the most promising for improving health outcomes in CF. Large well powered randomised controlled trials investigating specific probiotic strains and duration of probiotic supplementation on individual health outcomes in CF are required to further guide clinical practice.

Monitoring & Evaluation

If probiotic supplements are being consumed, it may be helpful to monitor subjective outcomes pre and post supplementation to assess whether they have been effective. The outcomes most amenable to monitoring in the clinical environment and which are important to individuals are functional gastrointestinal symptoms such as bloating, flatulence, abdominal pain and altered bowel motions.

Many probiotic strains do not permanently colonise the gut and at one to four weeks post cessation of the probiotic supplement, the probiotic strain/s are no longer recoverable in the faeces [720]. This is an important point to consider if recommending and reviewing probiotic supplements as they will likely need to be continued in the long-term for a sustained benefit [708]. Future work is required to develop practice resources based on region specific product availability, to assist clinicians to choose the best available probiotic product and regimen [707].

Practitioners are encouraged to ask about complementary therapy use and to be familiar with the evidence for both benefits and adverse reactions [721]. Potential interactions between traditional and complementary medicine and therapy use should be considered.

Practice Points PICO 15.1.1 and 15.1.2

Mechanism of action

- Probiotics are used as a therapeutic option to modulate the composition and actions of the gut microbiota.

Probiotic species, strain and dose

- Mechanism of action and efficacy are strain specific.
- Insufficient evidence to recommend any particular probiotic species or strain, single or mixed, as being superior for beneficial health outcomes in CF.
- The beneficial dose of probiotics varies depending on the particular species and strain used and the reported benefit – in most cases dose and duration should be based on manufacturer's recommendation.

Other considerations

- Impact on burden of treatment and medication adherence.
- Cost – probiotics can be expensive and not subsidised in Australia or New Zealand.
- Concerns regarding reported variability in quality control, efficacy and viability of probiotic microbes in different products.
- Storage – probiotics are sensitive to temperature, air, light and moisture and often require refrigeration.
- Probiotics are often marketed via their trade name (e.g. *Lactobacillus rhamnosus* is marketed as *Lactobacillus GG).*
- Recommend that if trialled, probiotics are taken for at least 4 weeks. If after this time they have no impact on symptoms, cease or trial an alternative preparation.
- Potential health benefits are thought to subside shortly after supplementation is ceased.
- Use probiotics with caution with high risk patients such as those with severe respiratory function.
- Care should also be taken administering probiotics to those with venous catheters due to risk of sepsis.

Translating into Practice

- Where a trial of a probiotic is indicated or requested, recommend (if possible);

  (i) A probiotic species and strain for which there is evidence for the particular health condition

  (ii) Reputable brand products which contain adequate therapeutic numbers of bacteria [707]

- Recommended dosage and duration of probiotic supplements will vary depending on the probiotic strain used and the health effect it is reported to have. In most cases dose and duration should be based on the manufacturer's recommendation.

- It is most likely that probiotics are required to be taken daily for best effect. Regular consistent intake may be required to achieve ongoing effects.

- The cost can be considerable and therefore it is important that people with CF understand the limitations of the available evidence which prevent clinicians from making specific product recommendations with certainty [707].

- Recommend that probiotics if trialled are taken for at least 4 weeks and if they do not work to try another brand or stop taking them [722].

- It is important to note that probiotic products may be identified, particularly from a marketing perspective, by their trade name; for example: LGG® rather than by the genera, species and strain.

- Probiotics are very sensitive to temperature, air, light and moisture and need to be stored correctly to ensure that they contain sufficient live organisms and remain viable. Read the package for storage instructions. Buy probiotics well before the expiration date as the longer a product has been sitting on the shelf the lower the number of viable microorganisms.

  The probiotic product should indicate the number of live cells of the probiotic strain/s it contains. For example: 6.5 billion or 6.5 x 10^9. The dose of a probiotic, instead of a number of milligrams or grams as used for a medicine in a tablet, is the number of cells or CFUs. CFUs stands for colony-forming units and is the way in which, the number of probiotic microbes is measured and described. It is an estimate of the number of "viable" bacteria or fungal cells in a sample.

15.2 Glutathione

C. Miles

Glutathione is a thiol-containing tripeptide, found in both plants and animals, with a number of important biological functions. It is the most abundant intracellular antioxidant and is synthesised by the liver from dietary cysteine sources [173]. Dietary sources of cysteine include meat, dairy, poultry, fish and soy-based products. Cysteine is a non-essential amino acid as it can be synthesised in the body.

Glutathione is a water-soluble antioxidant and therefore has important functions in the epithelial lining fluid of the lungs and intestines, the primary function of which is to inhibit free radicals [356]. Glutathione also plays a pivotal role in the immune system, particularly for chemotaxis and phagocytosis [356] as well as in ameliorating gastrointestinal inflammation[172].

Disease Aetiology

Reduced glutathione levels in the blood, neutrophils, lymphocytes and epithelial lining fluid have been reported in people with CF [173]. This profound glutathione depletion is believed to affect neutrophil recruitment to the lungs of people with CF and may contribute to the chronic inflammatory response described in these patients [173]. Total glutathione levels can be 10-50% of normal and therefore people with CF may not be receiving the full antioxidant or mucolytic benefits of glutathione [723]. Research has also shown that low levels of glutathione can lead to the release of

pro-inflammatory cytokines and in combination with affected neutrophil recruitment, may partly explain the excessive inflammation observed in CF [723].

A number of forms of glutathione supplementation have been trialled in humans including reduced glutathione and a glutathione precursor N-acetylcysteine. The precursor provides the amino acid cysteine for the replenishment of systemic glutathione. Both local treatments (inhalations) and systemic administration (oral formulations) of glutathione and N-acetylcysteine have been proposed to be of benefit to people with CF [356].

Assessment

DIET

Intake of glutathione supplements and reported effects in people with CF should be noted as part of a dietary assessment.

Intervention

Does antioxidant supplementation with oral glutathione or N-acetylcysteine improve nutritional and/or respiratory status in people with CF? PICO 15.2

[Grade C] Dietary supplementation with oral antioxidant glutathione or its precursor N-acetylcysteine may improve nutritional status in individuals with CF. There is inconsistent evidence to suggest that dietary supplementation of either of these treatments improves respiratory status. The currently available evidence does not support the use of glutathione therapy in people with CF [78,172-176].

Studies investigating antioxidant supplementation with oral glutathione or its precursor N-acetylcysteine in people with CF are heterogeneous in nature with varying formulations, doses, durations and outcome measures studied, making meta-analysis and consensus recommendations difficult [356].
There is limited evidence from a small case series study [176] including adults and children and a larger RCT including children only [172] that oral glutathione may improve weight percentile and BMI [176] and weight, height and BMI percentiles and z-scores [172].

Studies investigating effects of oral glutathione and its precursor N-acetylcysteine on improvements in respiratory function found inconsistent results for improvements in FEV_1 [174-176] pulmonary exacerbations [173,176] and sputum neutrophils [173,175]. There were no significant improvements in inflammatory markers with supplementation of oral glutathione or N-acetylcysteine [173-175].

Monitoring and Evaluation

Of the completed trials using glutathione and N-acetylcysteine supplementation in people with CF, a number of CF-related mild-moderate adverse events have been reported including gastrointestinal symptoms and pulmonary exacerbations [172-174,176]. Dauletbauev et al. (2009) reported one serious adverse event of a gastrointestinal bleed, however, it remains unclear as to whether this was related to N-acetylcysteine supplementation [174].

Practice Points PICO 15.2

Mechanism of action

- Glutathione is a water-soluble antioxidant.
- N-acetylcysteine provides the amino acid cysteine (non-essential amino acid) for systemic glutathione replenishment.

Sources of supplementation

- Dietary sources of cysteine include meat, dairy, poultry, fish and soy-based products.
- There is insufficient evidence to support the use of glutathione therapy in CF.

Other considerations

- Impact on burden of treatment and medication adherence

15.3 Coconut Oil

C. Miles & J. Heyward

Coconut oil has had a recent resurgence in both mainstream and CF diets with health claims reporting benefits of coconut oil in the prevention or mitigation of a wide range of health conditions. In terms of CF, the health claims relate specifically to the medium-chain triglyceride (MCT) properties of coconut oil and the hypothesis that coconut oil is more easily absorbed in people with pancreatic insufficiency.

Coconut oil is a type of saturated fat made up of two major saturated fatty acids; lauric acid and myristic acid. Lauric acid is technically a MCT and makes up approximately half of the fatty acids constituents in coconut oil. Whilst lauric acid is considered a MCT, it is metabolised differently and in digestion, behaves more like a long chain fatty acid. Approximately 4% of the fatty acids found in coconut oil behave as true MCT. Conversely, commercially manufactured MCT oils, which are generally derived from coconut or palm oils, contain approximately 95% MCT [724].

Assessment

DIET

Intake of coconut oil and reported effects in individuals with CF should be noted as part of a dietary assessment.

Intervention

Is there evidence that dietary supplementation with coconut oil improves nutritional status in pancreatic insufficient people with Cystic Fibrosis? PICO 15.3

[Ungraded] There is insufficient evidence to support a CF-specific recommendation

At present no experimental trials of coconut oil supplementation for improving health outcomes in individuals with CF have been conducted.

Monitoring and Evaluation

People taking coconut oil should be monitored for potential side effects such as loose bowel motions.

Practice Points PICO 15.3

Coconut oil composition:

- Lauric acid (45 - 48%) – medium chain triglyceride (MCT)
- Myristic acid (14 - 18%) – long chain triglyceride (LCT)

Lauric acid is considered a MCT, however, it is metabolised differently. In digestion, lauric acid behaves more like a long chain fatty acid.

Commercially manufactured MCT oils are generally derived from coconut or palm oils and contain approximately 95% MCT.

15.4 Herbal Supplements

C. Miles

The use of herbal supplements in people with CF is based upon the hypothesis that herbal products and their components have antioxidant and/or antimicrobial properties [725]. The most common herbal supplements that have been reviewed in the literature for people with CF are garlic, curcumin and ginseng.

Garlic has long been recognised among Chinese medicine and natural therapists for its medicinal and in particular antimicrobial properties. *In vitro* and animal studies have demonstrated that garlic has an inhibitory effect on the growth of *pseudomonas aeruginosa*. It has been hypothesised that garlic supplementation in individuals with CF and chronic *pseudomonas aeruginosa* infection may render this pathogen less virulent and more susceptible to the action of antibiotics [177,726].

Curcumin is a component of the Indian spice turmeric and has been extensively examined in the literature for its antioxidant and anti-inflammatory properties [727]. A number of *in vitro* and animal studies have investigated the role of curcumin in increasing CFTR-regulated channel activity in CF, with inconclusive results [728-735].

Ginseng is thought to have antioxidant, antimicrobial and immune-modulating effects [725]. In vitro and animal studies of ginseng supplementation have demonstrated that like garlic, ginseng can have an inhibitory effect on the growth of *pseudomonas aeruginosa* [736,737].

Assessment

DIET

Intake of herbal supplements and reported effects in individuals with CF should be noted as part of a dietary assessment.

Intervention

Is there evidence that dietary supplementation with specific herbal products or their components improves health outcomes in people with Cystic Fibrosis? PICO 15.4

[Grade D] There is no evidence that dietary supplementation with specific herbal products or their components improve health outcomes in individuals with CF [177].

A double-blind, placebo-controlled RCT in 26 children and adults with CF chronically infected with pseudomonas aeruginosa investigating the effect of garlic supplementation on lung function found a small improvement in lung function, weight and symptom score. These findings did not reach statistical significance [177]. Adverse events were reported to be mild and were either predictable side effects of garlic supplementation or intrinsic features of CF [177].

To date no human trials of curcumin or ginseng supplementation have been conducted in people with CF.

Monitoring and Evaluation

People with CF should be encouraged to discuss herbal supplement use with their treating team. If an individual with CF chooses to take herbal supplements, they should be monitored for both adverse and positive effects. Post lung transplant, there are a large number of drug-nutrient interactions between complementary and alternative medicines and medications used, therefore all supplements should be clinically indicated and confirmed with the treating team, including pharmacy, prior to commencement. Refer to Chapter 16 for more information.

Practice Points PICO 15.4

People with CF should be encouraged to discuss herbal and complementary therapies with their interdisciplinary CF team prior to commencing any form of supplementation. Specific enquiry by the CF pharmacist or dietitian may be helpful. Limited evidence surrounding dosing, safety or efficacy of most herbal supplements.

CHAPTER 16 LUNG TRANSPLANTATION

D. Hickling, A. Matson, M. O'Driscoll & C. Rawcliffe

Lung transplantation is a treatment option which can offer a survival benefit and improved quality of life for some people with end stage cystic fibrosis (CF) [738]. Optimising nutrition prior to lung transplantation can help to improve perioperative and post lung transplant survival outcomes [739-741].

There are 5 lung transplant units in Australia and New Zealand performing lung transplantation for people with CF – Fiona Stanley Hospital (WA), The Alfred Hospital (VIC), The Prince Charles Hospital (QLD), St Vincent's Hospital (NSW), and Auckland City Hospital (NZ). The Alfred Hospital hosts the Nationally Funded Centre for Paediatric Lung Transplant. Each unit is staffed by a interdisciplinary team specialising in transplantation. In Australia 31% (658 transplants) of bilateral lung transplants in adults (1992-2015) were for CF [742]. CF-related lung disease is the leading indication for lung transplantation in children [743-745] with over 50% of lung transplants in children 6-10 years and 69% for children 11-17 years being for CF [746].

In CF, lung transplantation is considered when life expectancy is poor despite optimisation of both medical and surgical management. The International Society for Heart & Lung Transplantation (ISHLT) 2014 Consensus document for the selection of lung transplant candidates [747] recommends that transplantation be considered for suitable people with CF who have a 2-year predicted survival of <50% and who have functional limitations. Timing of referral for lung transplant can be indicated by a number of factors, including worsening nutritional status despite supplementation, as outlined in the ISHLT 2014 Consensus document.

It is important for the CF and lung transplant teams to maintain open communication channels, with clear referral guidelines and pathways [2,3].

Early referral for lung transplant is essential to patient education and to allow adequate opportunity for modification of risk factors associated with worse outcomes [748]. Appropriate timing for referral of paediatric patients may be indicated for children on maximal medical therapy with a poor quality of life and a short predicted life expectancy [747].

The ISHLT consensus document also lists both absolute and relative contraindications to lung transplantation. Nutrition related contraindications include [747]:

ABSOLUTE CONTRAINDICATIONS:

- Class II or III obesity (body mass index (BMI) ≥35kg/m^2)
- Current non-adherence to medical therapy or a history of repeated or prolonged episodes of non-adherence to medical therapy

RELATIVE CONTRAINDICATIONS:

- Class I obesity (BMI 30.0-34.9kg/m^2), particularly truncal (central) obesity
- Progressive or severe malnutrition
- Severe, symptomatic osteoporosis
- Sub-optimal management of diabetes mellitus

International registry data reports the median survival time post lung transplantation in people with CF as being 8.5 years for adults [749]and 5.2 years for paediatric patients [746]. International Kaplan-Meier survival rates for adult lung transplant recipients with CF (January 1990 to June 2013) are 84% to 1 year, 48% to 9 years and 34% to 15 years [749].

16.1 Pre-transplantation

Pre-transplant care should be overseen by the local CF team [2]. Once a person with CF is listed for transplantation, close liaison between the CF team and the transplant team is essential [2].

Disease Aetiology

From a nutrition perspective, the period before transplantation is critical. Individuals with end-stage CF lung disease are at risk of significant weight loss as energy expenditure is raised. This is secondary to pulmonary sepsis, declining respiratory function and increased work of breathing associated with infective exacerbation [750]. Poor appetite and

difficulty eating/drinking due to shortness of breath can further impact a patient's ability to meet energy requirements. Mortality in underweight CF transplant recipients (BMI < 18.5 kg/m^2) is higher than in those of normal weight [19,739-741]. Increased mortality has been reported in underweight patients (BMI < 18.5 kg/m^2) on the lung transplant waitlist [19]. Class II Obesity (BMI ≥35kg/m^2) has also been found to contribute to the risk of mortality after transplant in both CF and non-CF recipients [739,741]. Of note some studies have not found an increased risk of mortality in people with CF who are underweight, when compared to a normal weight [751].

Assessment

Prior to transplantation listing, a thorough assessment by an interdisciplinary team specialising in lung transplantation is required. Aspects considered by the transplant team include respiratory function, rate of decline in lung function, age, sex, nutrition status, presence of other CF complications (CF-related diabetes status and management, osteoporosis, GOR, liver and renal function), quality of life, social support, adherence and the individual with CF's choice. A history of repeated non-adherence to medical therapy, or current non-adherence that is perceived to increase the risk of non-adherence post-transplantation, is an absolute contraindication to transplantation [747]. Chronic graft rejection due to non-adherence is particularly prevalent in adolescent patients and therefore needs to be addressed during transplant assessment [747]. For all patients, health outcomes post-transplantation may be negatively impacted by poor medication adherence [750,752].

The process of determining patient suitability for lung transplantation should include a comprehensive nutritional assessment, ideally by an experienced dietitian. Relevant information provided by the referring CF centre will enhance nutritional assessment.

Factors to take into consideration in handover, and in transplant nutrition assessment, are detailed in the sections (diet and clinical) below.

DIET

- Recent diet history and pancreatic enzyme replacement therapy (PERT) record
- CF-related diabetes: consider insulin/carbohydrate intake and ratio, as relevant
- Nutrition support: type, amount, mode (oral or enteral), frequency of use, tolerance, PERT dosage
- Adherence to recommendations regarding nutritional support

CLINICAL

GENERAL CONSIDERATIONS

- Check for nutrition impact symptoms: appetite, nausea, vomiting, early satiety.
- **Medications:** review micronutrient supplementation and adherence, gastrointestinal medications (prokinetics, anti-emetics, proton-pump inhibitors, acid suppressing agents and aperients), and complementary alternative medications.
- **Bone Health:** screening for osteoporosis should be undertaken prior to lung transplant [747,753] as severe and symptomatic osteoporosis is a relative contraindication for transplant [747]. This also allows earlier intervention to improve BMD status.
- **Comorbidities:** review control of comorbidities that may contribute to worsening nutritional status prior to transplantation.
    - **Gastrointestinal system** – GOR, Bowel habits, history of diarrhoea, constipation, distal intestinal obstruction syndrome (DIOS), infections with *clostridium difficile*, heightened risk of colorectal cancer (including previous investigations).
    - **Endocrine system** – CF-related diabetes: ensure recent screening (if not screened in last 12 months this will need to be addressed) and note date of diagnosis, duration of CF-related diabetes, management (frequency of BGL monitoring, insulin regimen and adherence, hypoglycaemia management, trend of HbA1c). Some transplant programs may have specific HbA1c targets.

ANTHROPOMETRY AND BODY COMPOSITION

- ISHLT guidelines outline severe or progressive malnutrition as a relative contraindication to lung transplant, therefore nutrition status needs to be assessed.
- Height, weight and BMI (including highest and lowest weights and recent weight history); local programs may have specific BMI or percentile targets for both children and adults.

- While the Subjective Global Assessment tool [754] has not been validated in the CF population, it may be one of many tools used to determine nutritional status.
- Where available: body composition, skinfold measurements, bone densitometry (DEXA), bioelectrical impedance analysis. See Chapter 5.

BIOCHEMICAL AND LABORATORY DATA

The following parameters should be reviewed:

- Fat-soluble vitamin levels and history
- Iron studies
- Oral glucose tolerance test. See Chapter 12 for diagnostic levels
- Liver and renal function
- Lipid profile

PSYCHOSOCIAL CONSIDERATIONS

- Supports to optimise food access and meal preparation
- Social and emotional issues affecting adherence to dietary advice and /or CF-related diabetes management
- Consider the impact of exercise and physical activity prescribed by physiotherapy on the individual's overall energy balance/requirements

Intervention

Prior to lung transplantation clinical care aims to optimise the patient's nutritional status [755]. Maintenance of lean body mass is a priority[756]. Aggressive nutritional support (via enteral feeding) may be required to counteract the rising energy requirements in patients with end stage CF lung disease. The option of transplantation and the need to meet specific nutrition-related or weight targets may assist the individual to prioritise nutritional improvements.

The following strategies should be considered:

- Optimising energy intake [755], progressively using nutritional strategies (behavioural, oral and enteral) See Chapter 6.
- Optimising efficacy of PERT. See Chapter 10.
- Optimising diabetes management if HbA1c >7.5%, as improving glycaemia may improve weight gain. See Chapter 12.
- Supplement fat soluble vitamins, as required with the goal of correcting to the normal reference range. See Chapter 9.
- Correcting mineral deficiencies (sodium, calcium, iron). See Chapter 9.
- Optimising nutrition management of gastrointestinal and hepatobiliary co-morbidities if present. See Chapter 11.
- Addressing nutrition-related factors contributing to low BMD and consider need for additional medical therapy prior to transplantation, including suboptimal calcium intake, vitamin D and K status. See Chapters 8 and 13.

Monitoring & Evaluation

Nutritional status should be assessed regularly while patients are on the transplant waiting list [755]. Good communication between both the treating CF team and the lung transplant team is essential.

16.2 Post-Transplantation

Post-transplant care is generally coordinated by the specialised transplant unit. Contact with the local CF team may be important to some individuals with CF to ensure that CF-specific medical problems can be addressed [2].

Nutritional management in the immediate post-operative period should focus on attaining adequate protein and energy intake [178]. Energy needs are increased in order to offset catabolism secondary to surgery, and anti-rejection

medication [178]. Some people will regain their appetite and eat well soon after surgery as breathing becomes easier, taste sensations improve, bowel function normalises and mobility improves. However, others experience anorexia and poor oral intake due to post-transplantation medications, taste changes, constipation, nausea and vomiting [178].

Aetiology of Post-Transplant Considerations

Post lung transplant the following nutrition-related issues may occur, and are important to consider:

BONE DISEASE (Chapter 13)

Reductions in bone density commonly occur following lung transplantation [753,757]. Corticosteroids and other medications that are required post-transplant may exacerbate pre-existing osteoporosis [753]l Osteoporosis is common post lung transplant and it appears to be more severe than that associated with heart, kidney, liver or bone marrow transplants [646]. The pathogenesis of osteoporosis post-transplantation appears to be multifactorial, with cumulative steroid doses being the major contributing factor.

BOWEL MANAGEMENT

Constipation and distal intestinal obstruction syndrome (DIOS) are common post lung transplant [758], with reported rates of up to 20% [563,564]. DIOS is particularly common in the early post-operative period [564,758,759]. Prevention and early treatment of constipation and DIOS is important and contributing factors to consider are outlined in Chapter 11. People 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 [564,760]. Early post-transplant post-operative pain management with opioids is also a contributing factor [759].

Clostridium difficile colonisation or recurrent infection is common in older CF patients and in the setting of immunosuppression, *clostridium difficile* colitis may lead to severe consequences [758,761]. People with CF are 2-3 times more likely than non-CF lung transplant recipients to develop *clostridium difficile* in the first 12 months post-transplant [758,762].

DELAYED GASTRIC EMPTYING

Delayed gastric emptying has been found in people with end stage CF both prior to [598] and post lung transplantation [598,760,763-765]. A number of factors can contribute to gastroparesis symptoms post-transplant, including pre-existing gastroparesis, surgical vagal disruption (at time of transplant or during fundoplication), diabetes management [597] and choice of immunosuppressant. Cyclosporin has been linked with slower gastric emptying while tacrolimus has prokinetic properties [597,766]. Gastroparesis symptoms can impact on a patient's ability to meet their nutritional requirements.

DIABETES (Chapter 12)

The post-transplant immunosuppressive regimen, which includes high doses of prednisolone and tacrolimus, cyclosporin or sirolimus, places individuals with CF at risk of developing new onset diabetes after transplant (NODAT) [767-769], or exacerbating existing CF-related diabetes [178]. This is secondary to both insulin resistance and insulin deficiency [178,767-769]. Prednisolone contributes to insulin resistance, where tacrolimus has been shown to reduce both insulin production and sensitivity [767-769].

NODAT rates have been reported as 20-32% of all patients post lung transplant [748,770-772]. In the CF population without pre-existing CF-related diabetes, NODAT has been reported to develop in 25-38% of individuals [769,771]. One Australian study found diabetes in 68% of CF lung transplant recipients, 63% of these patients had diabetes prior to transplant, with an overall NODAT incidence of 25% [771]. NODAT can be transient and is most common in the early period post lung transplant, with rates found to decrease to 19-20% at 12 months [748] and 17% at 24 months [770]. Corticosteroids, although reduced in dose in the 12 months post-transplant, are rarely ceased in lung transplant recipients and can contribute to NODAT persistence.

Irrespective of lung transplantation, CF-related diabetes is associated with a worse lung function, more chest infections, overall poorer nutrition and increased mortality [773]. The development of NODAT has been associated with an adverse impact on survival and an increased risk of graft rejection and graft loss, as well as an increased incidence of infectious complications [768]. In a retrospective case-control study including 25 CF patients almost all developed hyperglycaemia following lung transplant, but patients with diabetes prior to lung transplant had more complication related admissions to hospital and a higher mortality rate [774].

DRUG-NUTRIENT INTERACTIONS

Medications used to prevent complications, such as antibiotics, immunosuppressants and anti-fungal medications, can have marked side effects, including taste changes, nausea, vomiting and diarrhoea. Mycophenolate is commonly included in post-transplant immunosuppressant regimens and is associated with adverse gastrointestinal events, including diarrhoea [775-777]. A literature review showed adverse gastrointestinal events as the main reason for dose reduction, interruption and discontinuation of mycophenolate [778].

Organ transplant recipients are at a high risk for drug-nutrient interactions due to multiple medication regimens. Some herbal supplements have immunostimulant properties and modulate platelet aggregation. This may contribute to post-transplant complications or graft dysfunction [779]. Given the significance of these interactions, it is important to discuss the use of all supplements with the treating team, including a pharmacist, to avoid potential interference with a patient's immunosuppressant therapy. All supplements should be confirmed as being clinically indicated and confirmed with the treating team, including pharmacy, to ensure no drug-nutrient interactions before being commenced.

One of the most significant examples of drug-nutrient interactions involves grapefruit juice, which significantly increases the absorption of many currently available immunosuppressants, increasing the risk of drug toxicity [780]. Cyclosporin is highly lipophilic and sub-optimal enteral absorption may account for low bioavailability in people with CF [780]. 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 people with pancreatic insufficiency in order to achieve therapeutic concentrations [781].

Tacrolimus and cyclosporin may also be associated with hyperkalaemia. This is not always in the presence of acute or chronic renal failure and occurrence is not limited to early post-transplant, but may occur later. Hypomagnesaemia is a common side effect of tacrolimus and cyclosporin, therefore magnesium supplementation is routinely required from early post-transplant.

GOR (Chapter 11)

Gastrointestinal complications, including GOR, are more common post lung transplantation [542,757,763,764,782-784]. 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. GOR may contribute to a decline in lung function before and after lung transplant [542,785]. GOR can also be present as "silent reflux" where patients are asymptomatic. GOR has been found to be highly prevalent in lung transplant recipients and significant reflux has been identified as a risk factor for bronchiolitis obliterans syndrome (BOS) [786-788].

REDUCED IMMUNITY AND FOOD BORNE ILLNESS

Immunosuppressive therapies make organ transplant recipients more vulnerable to infections. It is widely accepted that these infections could potentially come from food contaminants, such as bacteria, viruses and parasites. Specific data on the risk associated with food-borne infections for Australian lung transplant recipients (with or without CF) is not available. However, review articles provide detail on the potential sources of foodborne and waterborne pathogens post-transplant, which may include Listeria, Salmonella, Crytosporidium, Giardia and Toxoplasma Gondii [789-792]. The World Health Organisation also lists immunosuppressed patients as being at risk of waterborne pathogens [793].

While listeriosis remains relatively rare across all populations, internationally increased rates have been found in transplant recipients [794-796]. A review by Silk et al. [794] showed case reports of foodborne listeriosis in immunocompromised patients. A French study of all listeriosis cases from 2001 to 2008 showed an increased risk of listeriosis in transplant recipients, with incidence rates of 7.91, compared to 0.39 per 100,000 overall incidence, but that transplant patients had the lowest fatality rate (6%) amongst risk groups assessed [795]. A Spanish study of all listeriosis cases in transplant patients from 1995 to 2007 found the same rate (0.12%) of listeriosis in lung transplant compared to all transplant types (0.12%). This study reported that while listeriosis in solid organ transplants is uncommon, it can cause a high mortality rate (26.7%) [797].

An Australian review of waterborne gastroenteritis outbreaks from 2001 to 2007 reported that while they are uncommon, the majority of drinking water sources are tank water or bore water related, with most common pathogens confirmed as salmonella, campylobactor, giardia or cryptosporidium species [798]. The study acknowledges most incidents are likely not reported, due to no medical treatment being sought [798]. The World Health Organisation Guidelines for Drinking Water Quality note that while rainwater is often as safe as drinking water, there are issues with pathogens and bacteria from the way it is stored, temperature of storage and where the water is collected from which is putting immunosuppressed individuals at risk [793].

Assessment

There are a number of potential nutrition related diseases and symptoms post-transplant that require assessment, and/or intervention and monitoring.

DIET

European and US recommendations for energy requirements in CF vary from 110-200% of energy needs for a healthy population [78,799]. In view of the lack of CF-specific evidence, energy and protein requirements immediately post-lung transplantation are based on recommendations for general surgical and other types of transplant patients. Use of surgical requirements provides a baseline for establishing minimum intakes (125-145KJ/kg, 1.2-1.5g/kg protein in adults). Nutritional status at time of surgery needs to be considered as malnourished patients are likely to have higher requirements than their well-nourished counterparts.

PERT

Recommendations for assessment explored in Chapter 10 are applicable post-transplant.

HYDRATION

It is important to check patient's usual home water supply, those with tank or bore water access will need further education regarding water safety.

COMPLEMENTARY ALTERNATIVE MEDICATIONS

Due to drug-nutrient interactions, complementary alternative medications are not recommended post-transplant, unless clinically indicated and confirmed with the treating team.

CLINICAL

GASTROINTESTINAL SYMPTOMS

Gastrointestinal symptoms should be regularly monitored, as per usual clinical assessment. In addition to this, due to the risk of gastroparesis directly post-transplant and/or post fundoplication, it is important to explore potential symptoms of gastroparesis, including nausea and/or vomiting, poor appetite, early satiety and poor volume tolerance. See Figure 16a for management algorithm and severity classification [800].

BONE DISEASE

Recommendations for assessment explored in Chapter 13 are applicable post-transplant. Regular BMD screening post-transplant will assist in identifying changes in BMD status (Chapter 13).

BOWEL MANAGEMENT

Assessment and stool samples in cases of diarrhoea post-transplant are recommended to assess for c.difficile infection [758,761]. Recommendations for assessment of constipation and DIOS explored in Chapter 11 are applicable post-transplant.

DIABETES (Chapter 12)

In the immediate post-transplant period blood glucose levels increase acutely, as a surgical stress response, necessitating post-surgical insulin in all patients. The potential for substantial weight gain in the first 1-2 years post-transplant likely contributes to insulin resistance in patients [801].

Factors to consider when assessing risk of NODAT:

- Age
- Ethnicity
- Weight history (consider history of obesity)[801]
- Family history of diabetes [801]
- Medications:
    - Immunosuppressant regimen (cyclosporin, tacrolimus and/or sirolimus) [770]
    - Dosage of corticosteroids (considering both basal doses and periods of prednisolone pulses at which time intermittent diabetes may occur) [801]

While optimal timing for testing for NODAT is yet to be determined, studies have indicated between 3-12 months is appropriate [748,801,802], with OGTT recommended at 3-6 months post-transplant [801]. This is after the immediate post-transplant period of higher immunosuppressant regimens, where transient diabetes may be present [748,802]. Regular fasting plasma glucose can be used to screen for impaired fasting plasma glucose levels. Bloom & Crutchlow [801] also recommend annual OGTT post-transplant due to the poor sensitivity of fasting plasma glucose when compared to OGTT.

In patients with known diabetes, regular BGL monitoring, three to four times daily is recommended.

BIOCHEMICAL AND LABORATORY DATA

FAT SOLUBLE VITAMINS

Monitoring should continue regularly post-transplant, a minimum of annually. See Chapter 8. Practice may vary across sites.

LIPIDS

Annual review is recommended post-transplant.

Intervention

DIET AND ENTERAL NUTRITION

Oral nutrition therapy post-lung transplantation can usually commence post-operatively following extubation. Early initiation of normal food or enteral nutrition after transplantation is strongly encouraged [755]. Intake can advance as tolerated to a regular diet, with accompanying PERT if pancreatic insufficient [178,756].

Enteral nutrition should be considered for patients with longer ventilation periods. The American Society for Parenteral and Enteral Nutrition (ASPEN) *Guidelines for Nutrition Support in the Critically Ill* support the use of enteral nutrition, when feasible within 24 hours of major surgery [803]. Supplementary enteral feeding may also be indicated if oral intake is insufficient to meet requirements [520]. Enteral feeding may be ceased when a patient can consume 65-75% of their requirements orally, the addition of oral supplements may be used to meet their overall requirements [520]. Some drugs used post-transplant require consideration regarding their interactions with food and may impact timing of enteral feeding regimens. See drug nutrient interactions below. Refer to Chapter 10 for considerations of PERT with enteral feeding.

The European Parenteral and Enteral Nutrition (ESPEN) *Guidelines for Surgery and Transplantation* [755] recommend the initiation of early nutrition support in the perioperative period, without delay:

- If it is anticipated that the person will be unable to eat for more than 7 days peri-operatively (even in people without obvious undernutrition).
- In people who cannot maintain oral intake above 60% of recommended intake for more than 10 days.
- Via enteral route except for the following contraindications: intestinal obstructions or ileus, severe shock, intestinal ischemia.

Consider pre-transplant nutritional status in decision-making about post-transplant nutrition support.

DELAYED GASTRIC EMPTYING

Prokinetics and dietary modification are recommended for the management of gastroparesis [597,598]. Treatment should include optimising glycaemic control (where relevant).

In terms of dietary modifications, fat and fibre are known to delay gastric emptying, so limiting these sources may be beneficial [597]. In cases of gastroparesis, digestion of liquids is usually preserved, therefore a liquid/pureed diet can improve tolerance to meet energy requirements [597].

In addition to dietary modification, prokinetics should be considered to improve gastric emptying and gastroparesis symptoms [597]. Long-term prokinetic use has been shown to safely improve delayed gastric emptying in lung transplant patients [804]. Whilst treatment with antiemetic agents will address nausea and vomiting, these mediations will not result in improved gastric emptying [597].

Awareness of drug interactions is vital as a number of prokinetics interact with transplant medication regimens, including domperidone with azithromycin, and erythromycin with tacrolimus/cyclosporin.

If oral intake is insufficient in an individual with post-transplant gastroparesis, then post-pyloric feeding (jejunostomy or naso-jejunal) should be considered [597]. Indications for enteral nutrition in cases of gastroparesis include unintentional loss of 10% or more of the usual body weight during a period of 3-6 months, and/or repeated hospitalisations for refractory symptoms [597]. Post-pylorus botox (botulinum toxin) injections, and surgical interventions including gastric pacemakers and pyloroplasty are relatively new treatment alternatives for severe gastroparesis, not resolved with diet and motility agents alone [597].

Post-pylorus botox (botulinum toxin) injections, and surgical interventions including gastric pacemakers and pyloroplasty are relatively new treatment alternatives for severe gastroparesis, not resolved with diet and motility agents alone [597].

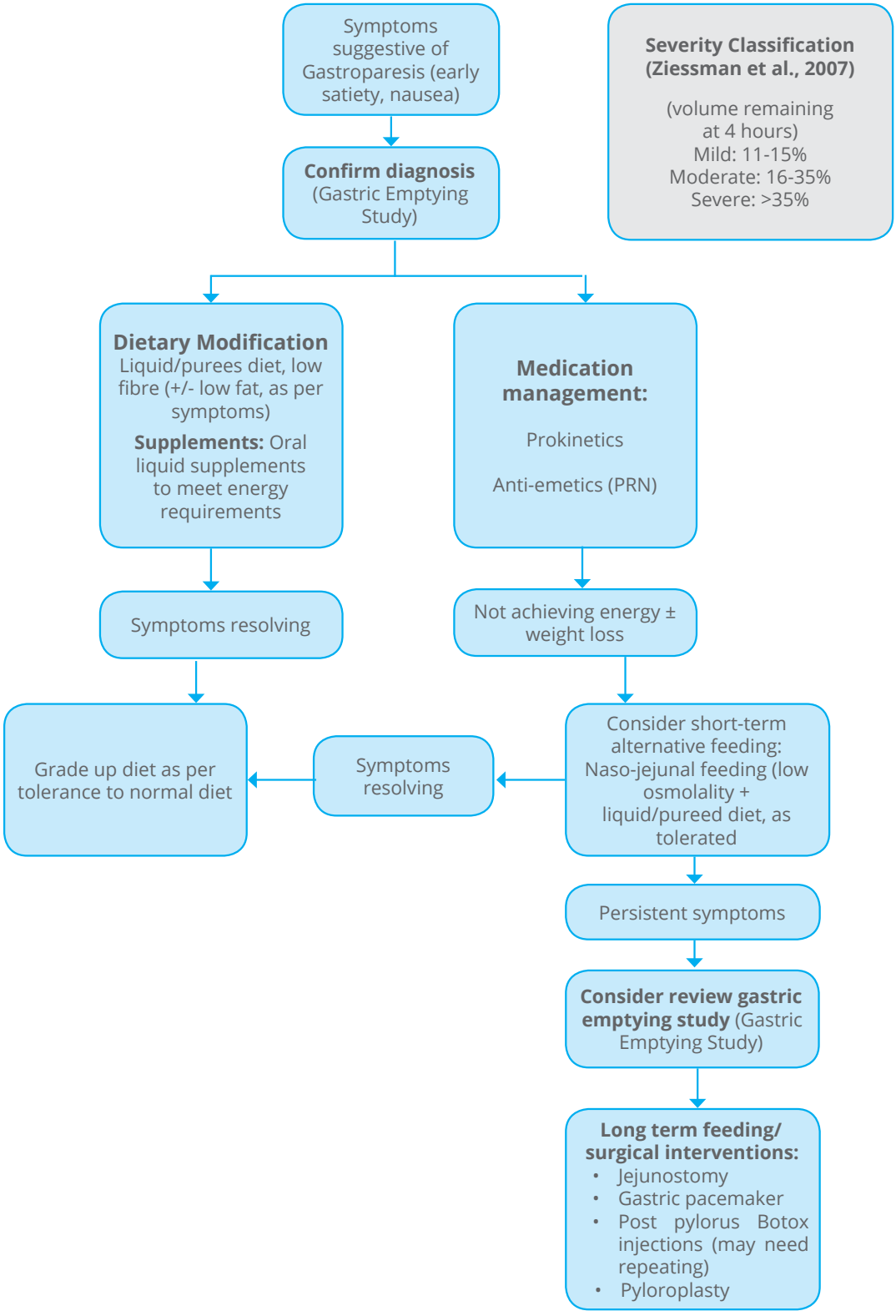

Figure 16a. Gastroparesis management algorithm for CF lung transplant (adapted from Camilleri et al., 2013)

DRUG NUTRIENT INTERACTIONS

Posaconazole suspension (liquid form), an anti-fungal medication, must be taken with a high fat meal to improve absorption [805] and achieve an adequate level; whereas posaconozole tablets can be taken with or without food [806].

Fasting times for oral medications should be considered when planning enteral feeding regimen timing. Intermittent feeding with breaks for oral or enteral tacrolimus administration and pre/post fasting is therefore more appropriate than continuous feeds. Regular electrolyte monitoring is important, and avoidance of a high potassium diet may be indicated in the presence of hyperkalaemia as explained in Aetiology [805,807]. Tacrolimus should be taken on an empty stomach either one hour before or two hours post food [807].

DIABETES

Management in the post-transplant period typically requires insulin and is predominantly due to the effect of prednisolone and tacrolimus. Three monthly monitoring of HbA1c is important. Regular review with the endocrine team is required with insulin doses needing to be adjusted with reduction in steroid dosage, adjustments in tacrolimus dosing and with intercurrent pulse steroids to manage rejection episodes or increase in steroids to manage episodes of infection.

Target HbA1c for NODAT is 6.5%, with a fasting BGL target of <6mmol/L, and post-prandial target of <8mmol/L [768]. This aligns with UK targets for type 1 diabetes of 6.5% or 48mmol/mol [641]. Specific targets for post-lung transplant patients with CF have not been established (see Chapter 12 for CF-related diabetes targets). Further research into NODAT in people with CF may alter HbA1c or BGL targets, however until then, an individualised approach to establishing HbA1c targets is recommended for CF patients with diabetes post-transplant, with consideration of hypoglycaemia and lifestyle factors [768]."

HYDRATION

Ensure patients maintain adequate hydration (up to 3-4L/day in adults, if required) as renal function may be adversely affected by immunosuppressive medications.

BOWEL MANAGEMENT (Chapter 11)

Where diarrhoea is persistent, and nutrition-related causes have been excluded, it is recommended to raise concerns with the treating lung transplant team to consider potential medication causes, such as mycophenolate. Recommendations for intervention for constipation and DIOS are explored in Chapter 11 and are applicable post-transplant.

REDUCED IMMUNITY AND FOOD BORNE ILLNESS

In Australia and New Zealand, there are no consistent dietary guidelines or food safety information provided to transplant recipients. In the absence of a standardised approach, discrepancies in the content and delivery of dietary education have been noted between centres [808,809].

If a food borne illness is contracted, it has been suggested that transplant recipients may experience more rapid onset of symptoms than the general population which can lead to severe dehydration, organ failure, sepsis or even death [789]. As a result, education on food safety with advice to avoid foods with a high bacterial load is generally recommended for solid organ transplant recipients. There is no current published evidence to support the efficacy of any food safety measures or dietary restrictions in reducing the risk of food-borne illness in lung (or other organ) transplant recipients. Similarly, there is no evidence regarding the duration that dietary restrictions are required. This may explain why food hygiene is not universally prioritised by patients.

Bore water and tank water that is untreated and not screened frequently for bacterial pathogens should be avoided due to risk of contamination [792]. Untreated water should be brought to rolling boil for 1 minute to kill all pathogens. Solar/ultraviolet water disinfection are a low-cost disinfection option for the treatment of water. Disinfection sanitises the water and reduces the risk of gastrointestinal infection. UV disinfection is particularly effective at removing cryptosporidium from water, whereas cryptosporidium is extremely resistant to chlorination alone. Further treatment at the point of consumption (reverse osmosis or filtration) may be applied to ensure better quality of drinking water and reduce health risks [793].

Useful resources for patient education can be located at:

- Queensland Health Nutrition Education Materials Online: "Safe Eating for Immunocompromised Patients" and "Food Safety" (https://www.health.qld.gov.au/nutrition/nemo_oncol)
- New South Wales Food Authority: (http://www.foodauthority.nsw.gov.au/foodsafetyandyou/life-events-and-food/low-immunity
- Victorian Better Health: https://www.betterhealth.vic.gov.au/health/healthyliving/food-safety-when-cooking

GOR

Anti-reflux surgery, such as a fundoplication, post lung transplantation, has been found to be safe and to result in an improvement in the rate of change in FEV_1 post lung transplant [785]. Two studies have shown improved long-term survival following anti-reflux surgery [783,810]. Some Australian lung transplant centres routinely perform 24 hour pH studies from three months post-transplant, when post-operative gastroparesis is likely to have resolved.
Texture modification can be required post fundoplication due to dysphagia-like symptoms. Education on early post fundoplication dietary modification should be provided by the treating dietitian. Short term nutritional supplementation may need to be considered to avoid weight loss. Chapter 11 provides a further summary of nutritional management strategies and on the medical management of GOR (including the use of PPIs for less severe GOR).

BONE HEALTH

In addition to adequate oral intake of calcium, prophylactic vitamin D and calcium supplementation can be recommended in patients with diagnosed osteopaenia or osteoporosis either in pre-lung transplant screening or post lung transplant [811,812]. Routine BMD is recommended to be undertaken 12 months post-transplant, annually thereafter for those with declining BMD, or every 2 years for patients with stable BMD. Patients with a T score <-1.5 require anti-bone resorptive medication (on the basis of steroid therapy) and a diet with sufficient calcium to meet RDI. Adequate vitamin D (>50nmol/L levels) [813] and weight-bearing exercise will also assist in maintaining bone health. See Chapter 13 for further information.

Monitoring & Evaluation

Long-term nutritional monitoring and advice is recommended for all transplant recipients [755]. After the initial post-surgical period and achievement of a healthy weight, routine nutritional management should be re-established.

ENERGY

After lung transplantation, energy requirements decrease as the work of breathing is reduced and infective exacerbations are fewer. An improved appetite due to the effects of anti-rejection medications and improved overall well-being assist in a person's ability to meet requirements orally. Dietary energy intake may need to be reduced in order to maintain a BMI of between 20 and 25 kg/m^2 in adults and normal growth trajectory in children. Dietary counselling to normalise eating habits and achieve a varied diet is important, particularly for those who have relied heavily on oral supplements or enteral feeding prior to transplant, and those with identified body image concerns.

Nutritional needs can change over time, particularly for those with a decline in health status, including longer-term post-transplant. In periods of infection or clinical deterioration, either acute or chronic, poor appetite or GI symptoms may contribute to increased nutrition requirements, reduced intake and/or weight loss. People with CF may require dietary modification including increasing energy intake either short-term or longer-term to prevent the development of malnutrition, including consideration of enteral feeding. This may include nasogastric feeding, or the consideration of insertion/reinsertion of a gastrostomy tube. Refer to Chapter 6 for nutritional interventions.

REMOVAL OF GASTROSTOMY

People with CF who have relied on supplementary enteral nutrition via a gastrostomy tube prior to lung transplantation can usually reduce the use of enteral nutrition as oral intake increases and nutritional status improves and if clinical status is satisfactory. Gastrostomy removal should be discussed between the individual with CF and the lung transplant team and assessed on an individual basis. Removal should be planned when the patient is clinically stable and able to consume adequate oral intake to maintain their goal weight without use of the gastrostomy [294,814,815]. The potential need for nutrition support via gastrostomy in the future should also be considered [814].

Prior to gastrostomy removal, it is recommended to seek a surgical and/or gastroenterological opinion regarding management [814]. Upon removal, the gastrostomy is likely to close within 2-7 days. Patients with tracts that do not heal within one week or with output from their stoma site should be referred for further medical and/or surgical input [814]. There is little to no evidence regarding permanent gastrostomy removal and closure in adults and/or CF lung transplant. However, clinical experience supports formal closure in patients with longstanding gastrostomies. Paediatric research in renal transplant has shown that gastrostomies in-situ for longer than one year are more likely to require surgical closure, with spontaneous closure more likely in those present for less than 12 months [816]. Other studies have supported that gastrostomies placed for over 11 months are less likely to spontaneously close [817,818].

DELAYED GASTRIC EMPTYING

Patients should be monitored for symptoms of gastroparesis, including early satiety, poor appetite, nausea and vomiting. If symptoms are present then a gastric emptying study may be indicated to formally diagnose gastroparesis.

DIABETES

Similarly to CF-related diabetes, regular self-monitoring of BGLs and HbA1c is recommended for all patients with NODAT, refer to Chapter 12.

VITAMINS AND MINERALS

Similar to energy needs, vitamin needs post-transplantation are often reduced. Serum vitamin A and E levels have been observed to be significantly higher in this population group, even after supplementation has ceased [819]. Factors possibly influencing vitamin levels include a decrease in pulmonary exacerbations, drug interactions and impaired retinol metabolism or increased hepatic synthesis of retinol binding protein [60,819]. Early monitoring of vitamin levels initially post-transplant (at 3-6 months post-transplant) will indicate when supplementation can be reduced or ceased, with ongoing annual review thereafter. Local protocols may vary in terms of cessation of vitamin replacement and timing of monitoring. Vitamin D supplementation may be continued in the presence of and/or for prevention of osteopaenia/osteoporosis, as per Chapter 8.

GOR

Monitoring for symptoms of gastroparesis post fundoplication and early intervention if identified is recommended to maintain nutrition status - see figure 16a. While symptoms are common in the first 3 months post fundoplication, the majority of patients' symptoms resolve by 1 year [597]. Monitoring for symptoms of gastroparesis post fundoplication and early intervention if identified is therefore recommended to maintain nutrition status.

DIOS

DIOS can recur later post-transplant [766]. Therefore, ongoing prevention strategies as detailed in Chapter 11 remain applicable post-transplant.

NUTRITION-RELATED LONG-TERM COMPLICATIONS

Increasing medical complications are being encountered with improved survival post-transplantation. Early recognition of these complications, and therapy directed to prevent these complications, may lead to reduced morbidity and mortality in patients who have undergone lung transplant. These complications have been comprehensively summarized for further information [820].

If other post-transplant complications or new unrelated conditions emerge which require additional dietary management or restriction of one or more dietary components, an individualised nutrition management plan should be developed which takes into account requirements for CF, lung transplant and the concurrent conditions. Examples include renal disease and malignant conditions. Input from both the transplant team and other teams including the dietitian may be required.

Lipids are routinely monitored post- transplant and if hyperlipidaemia is identified then dietary interventions are indicated (Chapter 7). With the achievement of a healthy BMI, ongoing education for healthy eating choices should be encouraged, including consideration of appropriate dietary fat sources and limiting saturated fat intake.

CHRONIC KIDNEY DISEASE

Chronic Kidney Disease (CKD) is a common complication after non-renal solid-organ transplantation. The risk of CKD is influenced by many factors, some of which have a direct impact on how such patients are treated in the pre-, peri- and post-transplantation settings. The most common cause of renal failure is calcinuerin inhibitor (CNI) nephrotoxicity [821], CNI medications forming part of patient's immunosuppressant regimen. Monitoring of renal function, and diet modifications to manage impaired renal function should be on a case by case basis and in consultation with specialist renal services. Evidence based guidelines for nutritional management of chronic kidney disease in Australia and New Zealand are available [1].

BONE HEALTH

Due to the ongoing requirement for medications contributing to osteoporosis, including tacrolimus and corticosteroids, regular BMD testing is recommended as outlined in the Interventions section of this chapter [753,759].

CHAPTER 17 IMPLEMENTING, EVALUATING AND MAINTAINING THE GUIDELINES

N. Saxby, J. Anderson, N. van der Haak & S. Kumar

Evidence-based practice in health care is the integration of best research evidence with the clinical expertise of health professionals while respecting patients' moral values and beliefs. The generation of best research evidence, through systematically developed best practice statements and evidence-based recommendations, is merely the first step in achieving best practice in nutritional care for Cystic Fibrosis. With the emergence of implementation science, it is evident that evidence-based recommendations should be supported with evidence-based dissemination and implementation strategies. Once the '2017 Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand' are published, the guidelines must be disseminated to all those stakeholders who are involved in Cystic Fibrosis care. The implementation of the guidelines within individual health care contexts will be led by local health professionals, who will determine how best to implement the guidelines.

Planning for implementation of the '2017 Nutrition Guidelines for Cystic Fibrosis in Australia and New Zealand' has been undertaken in parallel with guideline development. Additionally, the members of the authorship and interdisciplinary expert groups represent over 95% of specialist CF centres in Australia and NZ. Thus, the creators of the guideline are themselves the target users, a unique situation that offers several implementation advantages. Benefits include an already high awareness of, and agreement with, the guideline recommendations. To further aid uptake of the guideline recommendations a multi-component implementation strategy is also planned.

Dissemination and Implementation Plan

A multi-faceted strategy will be used by which the guidelines can be disseminated and implemented. These include:

- **Distribution of educational materials** – The guidelines will be made available to target users via posting on websites of TSANZ, CFA and CFNZ. The guidelines will be registered with Australian (NHRMC clinical guideline registry) and international (Guideline International Network) guidelines registries. Under the auspices of TSANZ, the guideline authorship group will send written notification of the '2017 Guidelines' availability to all CF centres in Australia and NZ. All correspondence will be addressed to CF centre director and the specialist CF dietitian, where details are known. As means of engaging with the wider community, a link to the guidelines will be disseminated to relevant universities, colleges, societies, associations and other professional organisations. A publication in a peer-reviewed journal is also proposed which will highlight any recommended changes to nutritional care in Cystic Fibrosis. A media release and notification in CFA/CFNZ newsletters will also be undertaken.

- **Patient-mediated** – Key guideline chapters will be accompanied with resources targeted at patients, their families and communities. This will ensure the guidelines and its recommendations can be readily consumed by patients, their families and communities and will assist in shared decision making between health professionals and the consumer.

- **Educational meetings** – Educational meetings in the form of interdisciplinary working groups, conferences and workshops, including virtual options such as webinar, could be considered. Educational meetings can be particularly useful in local health care contexts when implementing guidelines to identify and address local barriers and enablers. A tool kit for implementation could be developed which may assist local implementation initiatives.

- **Use of opinion leaders** – Local opinion leaders could be used to facilitate local implementation initiatives. Opinion leaders could utilise the educational resources to facilitate local implementation and practice change initiatives. Local opinion leaders could also act as mentors to assist in and support other health care professionals during the implementation and practice change process. Resources such as accompanying outpatient clinic, inpatient and nutritional assessment forms may also be used by opinion leaders during this process.

- **Audit and feedback** – Audit and feedback could be used as part of local implementation initiatives to assess and describe practice and behaviour. Findings from the audit can then be used to reinforce and change practice and behaviour, as required. Key indicators on organisation of care and clinical care should be made available which will underpin audit and feedback initiatives.

- **Reminders** – Reminders for health care professionals, patients and other health care stakeholders through posters, emails, messages, leaflets, stickers, coloured charts, and newsletters should be considered. If and where possible electronic reminders may also be considered, embedded as part of processes of care, once areas for quality improvement have been identified at local health care contexts.

With the emergence of implementation science, the evidence base on "how to" implement evidence into practice is growing at a rapid pace. However, much of the literature on dissemination and implementation strategies suffers from serious methodological flaws. While there is some evidence to support the multi-faceted strategies outlined above, which strategy works for whom, when and how continues to be a *"black box"*. The gains achieved by these multi-faceted strategies could be described as modest at best and this can be explained by the fact that a number of contextual factors at the individual, organizational and system level exist, resulting in additional challenges to implementation. Therefore when considering implementation, it is imperative to consider local and contextual issues and select targeted strategies that are likely to meet local requirements.

It is strongly recommended that any implementation initiative is underpinned by a systematic and deliberate approach to improve nutritional care for Cystic Fibrosis. The systematic and deliberate approach could be informed by the following - identification of key stakeholders, adequate resource allocation, audit of current practice, identification of barriers and enablers to guideline implementation and use, development of implementation tools, determination of implementation strategies that are likely to affect practice and behaviour change, development of implementation plan and pilot testing to verify its appropriateness and feasibility and relevant modifications, as required. As evidence-based practice builds on shared decision making with patients, implementation strategies should also consider nutritional care for Cystic Fibrosis which builds on local cultural and geographical needs and requirements.

It is particularly important to consider barriers and facilitators to implementation of the guidelines. Potential barriers include

- Time and cost of implementation of the guidelines at a local level
- Lack of resources – both staffing and physical (e.g. certain medications listed)
- Disagreement among practitioners and people with CF around recommendations made
- Inadequate communication regarding the existence of the guideline

Potential facilitators to overcome these barriers are listed above.

WORKSHOP

An implementation workshop was held on the 20th of November 2016 in Melbourne, hosted by the TSANZ. It addressed guideline content, recommendations, feedback from public consultation and implementation into clinical practice.

Evaluation Plan

The effectiveness of the *'2017* Guidelines' will be assessed via a survey of dietetic practice and nutritional management of CF in Australia and New Zealand, similar to the 1998, 2005 and 2010 (unpublished) practice surveys [179,180,822], with the addition of items specifically addressing:

- Changes in clinical practice and health outcomes as a result of implementation of the guidelines
- Compliance with the guidelines

It is anticipated that this survey will be conducted within 1 to 2 years after the guidelines are approved by NHMRC, and will be completed by a post graduate research student. Evaluation support will be provided by the School of Allied Health staff at La Trobe University.

Guideline Review and Update

A full guideline update is planned for 2022. The TSANZ, DAA and DNZ will convene a group of experts to undertake the review. Until 2022, the co-chairs and project facilitators of the *'2017 Guidelines'*, via the Clinical Care and Resource Sub-Committee of the TSANZ, will be the contacts for major issues, events or practice changes.

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Recommendations for Future Research

Further research and/or the expert consensus is required to make recommendations for people with CF regarding:

- Use of behavioural modification strategies in adults (eating and mealtime)
- Enteral feeding – the most effective regimen and ideal timing for initiation of enteral feeding for someone who is undernourished
- The role of fibre in gastrointestinal health
- How to monitor vitamin A, E and K levels (both frequency and laboratory tests used) and the safe upper limits of vitamin A, E and zinc supplementation
- The appropriateness of routine supplementation of fat soluble vitamins in pancreatic sufficient patients
- The goal level of serum vitamin D with or without bone disease
- The ideal vitamin D dosing regimen to correct deficiency
- Appropriateness of high dose vitamin D (i.e. ≥ 50 000IU) supplementation to correct deficiency
- Long-term implications associated with phthalate exposure via PERT
- Nutritional considerations for colon cancer screening in CF
- Management of vitamin A and K supplementation in people with CF-related liver disease
- How to administer PERT with enteral feeds, including in those how are nil by mouth or have an oral aversion
- Optimal timing of PERT
- Use of proton pump inhibitors in conjunction with PERT to improve efficacy
- Specific PERT doses to support optimal fat absorption, and the safe maximum dose of PERT that can administered, and ideal doses
- The best tests to assess PERT efficacy
- The role of gastrointestinal and other nutritional outcome measures in individuals with CF receiving genetic modulator therapies
- Long term nutritional considerations (e.g. energy, salt intake) for people on genetic modulator therapies
- Complementary nutritional therapies for CF (e.g. coconut, turmeric, antioxidant, probiotics)
- Potential long term effects of overweight and obesity in the CF population, including balance of fat intake
- New treatments targeting nutritional complications of CF (e.g. anti-osteoporotic agents, anti-inflammatory agents, anabolic therapies, appetite stimulants)

See Chapter 2 for proposed consensus plans.

CHAPTER 18 EVIDENCE MATRICES

Chapter 4 **Service Delivery**

Chapter 4 Q4.1.1 What is the level of dietetic service required for people with CF?
No evidence available

Chapter 5 **Nutrition Assessment**

This chapter is a narrative of the CF nutrition assessment process and considerations.

No clinical questions and PICOs were identified for this chapter.

Chapter 6 **Nutrition Interventions**

6.1 Undernutrition

Chapter 6 Q6.1.1 Compared to standard nutritional care, do behavioural interventions around food and mealtimes improve behaviours, diet variety, and weight or nutrition status in children with CF?		
NHMRC Grade for recommendation: Grade B		
Evidence statement: There is some evidence to support the beneficial effect of behavioural modification techniques to help improve child behaviours during meal time and/or family functioning. Evidence that improved behaviours then results in increased energy intake and/or weight is conflicting. Providing parents with behavioural strategies and nutrition education has been shown to be more effective in improving energy intake and growth of children than nutrition education alone. A limitation to this evidence base is that the vast majority of research comes from the same group in the USA.		
Evidence base	**B** Good	5 studies, various sample sizes. • 1 level I study, meta-analysis positive quality • 2 level II studies (n= 78, n=79), RCTs both positive quality • 1 level III-2 comparative case control study (n=67 trial group), comparison sample (n=346), neutral quality • 1 qualitative study (n= 8), neutral quality
Consistency	**C** Satisfactory	2 Studies reported on parent and child behaviours during meal time and/or overall family functioning. • Family functioning appears to be positively related to weight status and positive eating behaviours. 3 Studies reported on energy intake and/or anthropometric measurements. • Mixed results for use of behavioural intervention and improved energy intake and positive changes in anthropometric measurements.
Clinical impact	**C** Moderate	The evidence is directly relevant to the clinical question. • Potential benefits to energy intake and anthropometric measurements. • May require additional resourcing (e.g. psychology of family therapist support).

Generalisability	**B** Good	All studies completed in paediatric population groups in the USA and are translatable to an Australian context. Most data relates to children aged 1 to 12 years, may not be applicable to older adolescents.
Applicability	**C** Moderate	Many of these studies were undertaken in populations where newborn screening did not take place. Thus the early years journey in the study populations, age of diagnosis, time of treatment commencement and the severity of undernutrition is likely to be quite different from the current populations in Australia/New Zealand. Dietitians and other practitioners may require additional training in behavioural modification techniques around food and mealtimes.

Chapter 6 Q6.1.2 When should behavioural interventions around food and mealtimes be considered for children with CF?

NHMRC Grade for recommendation: Grade C

Evidence statement: Evidence suggests that behavioural modifications should be commenced early in life before typical childhood maladaptive eating behaviours become an ongoing issue. Early intervention may assist parents in dealing with problem mealtime behaviours in order to change a sense of concern and maximize food intake. In addition, evidence suggests that these strategies should continue throughout all ages of childhood.

Evidence base	**C** Satisfactory	Three studies, small to medium sample sizes • One level III-2 study (n=68), positive quality • One level III-3 study (n=34), neutral quality • One level IV study (n=8), neutral quality
Consistency	**B** Good	Three studies show that disruptive mealtime behaviours and inappropriate parental responses often start very early in life. One study showed that parents were still using behavioural management strategies learnt when their child was young years later.
Clinical impact	**C** Satisfactory	The evidence is suggestive that inappropriate mealtime behaviours can commence early in childhood, and that parents often do not have the skills to deal with these behaviours. Starting behavioural modification interventions early is achievable and low risk.
Generalisability	**C** Satisfactory	All studies completed in young children and children of primary school age, thus results are not transferrable to adolescents and adults. • Studies completed in USA are generally comparable to Australia and New Zealand CF populations.
Applicability	**B** Good	Many of these studies were undertaken in populations where newborn screening did not take place. Thus the early years of the study populations, are likely to be quite different from the current populations in Australia /New Zealand.

Chapter 6 Q6.1.3 Do appetite stimulants, megesterol acetate and cyproheptadine, improve nutritional status in CF?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: As per the findings of a Cochrane review, there is some evidence from three small studies to suggest that appetite stimulants may improve weight and appetite for people with CF. However, there is inadequate evidence regarding adverse side effects and safety with longer term use. As a result, the routine use of appetite stimulants is not recommended to improve nutrition status in CF.		
Evidence base	**C** Satisfactory	1 Cochrane systematic review of the available evidence (Level 1 – positive quality). • Includes 3 small randomized and quasi-randomised control trials • N=47 participants across the 3 studies
Consistency	**B** Good	Findings were generally consistent amongst the studies included in the systematic review: • Weight z-score significantly improved across all trials after 3 months of use. • Weight significantly improved after 6 months with megesterol acetate use in one study. • No significant impact on pulmonary outcomes (FEV_1 percent predicted). • A statistically significant increase in the proportion of people with CF with an increased appetite.
Clinical impact	**C** Satisfactory	The evidence is directly relevant to the clinical question. • Potential benefits to nutritional status are highly relevant to people with CF. • The lack of evidence regarding potential side effects and safety limits the overall assessment of clinical impact.
Generalisability	**C** Satisfactory	Most studies are conducted in countries with generally comparable populations. • Includes both paediatric and adult population (note the breakdown in numbers between the paediatric and adult population weren't always reported).
Applicability	**C** Satisfactory	Evidence somewhat applicable to the Australian CF population: • 2 of the 3 studies from the US with a similar CF population to Australia

Chapter 6 Q6.1.4 Does the use of recombinant growth hormone improve nutritional status in pre-pubertal people with CF?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: As per the findings of a Cochrane review, there is some evidence from 4 studies to suggest that growth hormone may improve height, weight and lean tissue mass for the pre-pubertal CF population. However, the currently body of evidence only looks at short term use (6-12 months). Longer term randomised control trials are required prior to recommending the routine use of growth hormone for the CF population.		
Evidence base	**C** Satisfactory	1 Cochrane systematic review of the available evidence (Level 1 – positive quality). • Includes 4 randomized and quasi-randomised control trials • N=161 participants across the 4 studies

Consistency	**B** Good	Findings were generally consistent amongst the studies included in the systematic review: • Modest improvements in height, weight and lean tissue mass. • Improvement in lean tissue mass. • No consistent impact on lung function, muscle strength, clinical condition and/or quality of life. • No effect on glucose metabolism and doesn't increase the chance of developing CFRD.
Clinical impact	**C** Satisfactory	The evidence is directly relevant to the clinical question. • Potential benefits to nutritional status are highly relevant to person with CF. • Little evidence to support an increase in quality of life.
Generalisability	**C** Satisfactory	Most studies are conducted in countries with generally comparable populations. • All studies included pre-pubertal people with CF (<25 years of age). • All participants had weight and height percentiles between the 10-25th percentile for age and gender. • Most subjects were clinically stable.
Applicability	**C** Satisfactory	Evidence somewhat applicable to the Australian context.

Chapter 6 Q6.1.5 Is there any rationale for the use of commercial oral nutritional supplements in addition to food and mealtime strategies to improve nutritional intake, weight or pulmonary function in CF?		
NHMRC Grade for recommendation: Grade B		
Evidence statement: There is consistent evidence from studies of reasonable quality to suggest that oral nutrition supplements are unlikely to result in improved BMI outcomes, nutritional intake or pulmonary function in individuals with CF.		
Evidence base	**B** Good	7 small – medium sized studies • 2 level I studies – both Cochrane reviews of RCTs or quasi-RCT's, • 1 level II study (n=102) - RCT • 1 level III-1 (n=13) • 3 level IV studies – retrospective case series (n=75), two cross sectional studies (n=47 and n=94)
Consistency	**B** Good	Overall good consistency with most studies reporting a limited benefit regarding the use of oral nutrition support. • Two paediatric studies reported on BMI outcomes with only one of the two studies finding a positive correlation between supplementation & nutrition status. • Four combined paediatric and adult studies reporting no improvement in BMI. • Two studies looked at lung function and oral nutrition supplements. No statistically significant benefit was reported. • Three studies looked at nutritional intake while on oral nutrition supplements. Overall consistent findings with 2/3 studies reporting no improvement in total energy intake while on oral supplements.
Clinical impact	**C** Moderate	The evidence is directly relevant to the clinical question. • The likely lack of improvements in intake, BMI and lung function are relevant to people with CF and their decision making process around oral nutrition support.

Generalisability	**C** Satisfactory	• Some studies are only in the paediatric population. Those looking at both the adult & paediatric population don't extrapolate results by age. Most studies are conducted in countries with generally comparable populations. • Results are seen in people with CF with varying severity of lung disease (>30% FEV1), which is true of our population. • Inclusion/exclusion criteria are not outlined in most studies making it difficult to gauge a clinical picture of the study population. It is hence difficult to assume generalisability.
Applicability	**B** Good	The indications for oral nutrition support initiation and supplementation regimens used in the studies (though somewhat poorly described) generally appear to match current accepted practice in the Australian context (individualized supplement choice based on individual preference and tolerance between 1-3 supplements per day or as accepted in addition to normal high energy intake).

Chapter 6 Q6.1.6 Should enteral feeding be considered to improve nutrition outcomes for people with CF?		
NHMRC Grade for recommendation: Grade B		
Evidence statement: There is consistent evidence to indicate that enteral feeding improves markers of nutritional status such as weight, BMI and BMI z score in adults and children with CF. In most studies, the best outcomes appear to be achieved within the first 6-12 months of feeding. Improvements in weight were not necessarily exponential or sustained over time, appearing to plateau or decline at the 2, 3 or 4 year interval. The quality of the evidence base is poor, and future research should be by way of well-designed studies, multicentre in nature and minimising bias.		
Evidence base	**D** Poor	10 small studies: • 2 level III-2 studies – one comparative (n= 15) and one case control (n= 48), both with concurrent controls • 3 level III-3 studies- two retrospective cohort (n= 46, n= 40), one interrupted time series without a parallel control group • 5 level IV studies – three retrospective case series (n=14, n=11, n=7) , one case series with pre/post-test (n=37), one systematic RV (n=17 studies
Consistency	**A** Excellent	Excellent consistency amongst studies looking at paediatric, children or combined paediatric & adult data. • Various anthropometric markers were considered when looking at nutrition outcomes, including weight gain (% total body weight), BMI, weight for age z-score and BMI z-score. • Most studies reported an improvement in the anthropometric parameter studied, with the biggest improvements seen in the first 6-12 months.
Clinical impact	**A** Excellent	The evidence is directly relevant to the clinical question. • Potential benefits to nutritional status are highly relevant to people with CF. • The duration of the therapy required is achievable (most studies report on benefits within the first 6-12 months and follow for up to 4 years) and the benefits outweigh the risks.

Generalisability	**A** Excellent	Evidence directly generalisable to target population. • Studies in both paediatric & adult population. • Most studies are in Australia, UK and US giving comparable populations. • Study demographics with varying lung function, mostly pancreatic insufficient, either existing malnutrition or some level of nutritional failure or risk despite the implementation of nutritional therapies.
Applicability	**A** Excellent	Evidence directly applicable to Australian healthcare context as resources required to achieve outcome in the studies e.g. staff time and expertise, EN supplies, feed type, equipment are all available in the Australian setting. • The indications for initiating enteral nutrition support and feeding regimens used in the studies matched current accepted practice. • Australian cultural factors would be similar in studied populations and Australian populations.

Chapter 6 Q6.1.7 Should enteral feeding be considered to improve pulmonary status in people with CF?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: [Grade C] There is inconsistent evidence from small, low quality studies to suggest that enteral feeding may improve pulmonary function in someone with CF. Overall, due to the heterogeneity of baseline lung function across studies and the likely progressive nature of lung function decline over study periods, the application of studied regimens could not be expected to generate a predictable outcome in our populations.		
Evidence base	**D** Poor	9 small studies: • 1 level III-2 study – Interrupted time series (n= 17) with concurrent controls • 3 level III-3 studies - retrospective cohort study (n= 20 cases & controls), two interrupted time series without a parallel control groups (n= 21 & n=46) • 5 level IV studies – three retrospective case series (n=14, n=11, n=7), one case series with pre/post test (n=37), one systematic RV (n=17 studies)
Consistency	**D** Poor	Overall, despite studies having similar designs, populations and outcome measures, the results are inconsistent across studies varying from significant improvement in lung function to significant decline. • 3 studies indicate increased FEV1 • 2 studies found no change in FEV1 • 2 found a decline in FEV1 • 2 studies suggest minimal difference in IV antibiotic use and another suggests an increase in IV antibiotic days
Clinical impact	**C** Moderate	The evidence is directly relevant to the clinical question. • Potential benefits to lung function are highly relevant to people with CF; the interventions required are achievable and relatively low risk. However given the variability in results across studies it is difficult to predict substantial clinic impact.

Generalisability	**B** Good	Most studies are in children or adolescents only 3 include adults and results in children would not be transferrable to an adult population. Most studies are in Australia & US giving generally comparable populations. Results seen in people with CF with varying severity of lung disease- which is true of our populations. Given the intervention of enteral feeding most studies explain or imply their study population has existing undernutrition or a risk of developing undernutrition- this is relatable to our enteral fed populations.
Applicability	**B** Good	Evidence directly applicable to Australian healthcare context as resources required to achieve outcome in the studies are all available in the Australian setting. These include staff time and expertise, EN supplies, feed type and equipment. The indications for EN initiation and feeding regimens used in the studies (though somewhat poorly described) generally appear to match current accepted practice in the Australian context. Cultural factors would be similar in studied populations and Australian populations given the bulk of studies are in Australia, US assumption can be made that attitudes to health and compliance would be similar in these settings.

Chapter 6 Q6.1.8 When should enteral feeding be introduced for people with CF?
No evidence available

Chapter 6 Q6.1.9 What is the ideal enteral feeding regimen for people with CF?
No evidence available

Chapter 6 Q6.1.10 What are the risks associated with enteral feeding in CF compared to the general population?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: There is satisfactory, consistent evidence from low quality studies to suggest that enteral feeding in CF is safe, with no major complications or mortality reported in subjects. Studies describe a range of minor complications associated with enteral feeding in CF, the most common being stoma site issues or reflux.		
Evidence base	**D** Poor	9 small studies: • 2 level III-2 studies – one comparative (n= 15) and one case control (n= 48), both with concurrent controls • 3 level III-3 studies - a retrospective cohort study (n= 20 cases & controls), two interrupted time series without a parallel control groups (n= 21 & n=46) • 4 level IV studies – all retrospective case series (n=14, n=11, n=7), one case series with pre/post-test (n=37)

Consistency	**B** Good	Overall consistent evidence between studies. Across all studies, there was no evidence of major complications or mortality reported. The main limitation to consistency is the heterogeneity of outcomes that studies looked at or looked for in their populations. This is related to differences in study aims and ability of retrospective data collection to target outcomes of interest. • 2 studies suggested a link with CFRD. • 4 studies commented on an increased risk GIT issues (i.e. abdominal pain & reflux). • 8 studies reported at least one subject with stoma issues (i.e. itchiness, redness, pain and milk stoma leakage). • 2 studies found no pulmonary exacerbation or aspiration. • 1 study commented on body image and acceptance. • 2 studies discussed a risk of poor adherence to enteral feeding. • Other identified risks included bed wetting, perhaps due to the larger feed volumes and feeding pump difficulties.
Clinical impact	**C** Moderate	The evidence is directly relevant to the clinical question. The results are clinically important to the CF population as it allows them to weigh up risks vs. benefits of enteral feeding. • Studies had reasonably long data collection periods of 6 months to 4 years, thus there would be sufficient time to pick up major complications of enteral feeding if they did exist.
Generalisability	**B** Good	The evidence is directly generalisable to the target population however most studies are in the paediatric population and are not necessarily transferrable to the adult population. Most studies are in Australia and the US giving comparable populations.
Applicability	**A** Excellent	The evidence is directly applicable to the Australian healthcare context as resources required to achieve outcome in the studies. • The indications for EN initiation and feeding regimens used in the studies (though somewhat poorly described) generally appear to match current accepted practice in the Australian context. • Cultural factors would be similar in studied populations and Australian populations. Given the bulk of studies are in Australia, US assumption can be made that attitudes to health and compliance would be similar in these settings.

6.2 Overweight/obesity

This chapter is a narrative of the CF nutrition considerations for overweight and obesity in CF.

No clinical questions and PICOs were identified for this chapter.

Chapter 7 **Macronutrients**

7.1 Energy, Protein, Fat and Fibre

Chapter 7 Q7.1.1 Are energy requirements increased in the CF population compared to the general population?		
NHMRC Grade for recommendation: Grade D		
Evidence statement: Within the inclusion period for this review, there was no evidence to guide energy requirements for the entire CF population. The evidence from observational studies refers mostly to infants, children and young people <21 years. Until further evidence is available, it is recommended that health professionals continue to be guided by consensus guidelines when recommending energy targets for people with CF.		
Evidence base	**C** Satisfactory	A combination of level III and IV studies were included for review. 4 Level III-2 studies • Children: n=15, n=134; positive quality • Children & adults: n=12; positive quality • Adults: n=21; neutral study 5 Level III-3 studies • Infants: n=46; neutral quality • Children: n=17, n=15, n=12; neutral quality • Adults: n=11; neutral quality 5 Level IV • Children: n=16, n=56, n=86; neutral quality • Children & adults: n=16; positive quality and n=38; neutral quality
Consistency	**D** Poor	Overall lack of consistency in study methodology and outcome measures. Each study looked at one (or more) of the following on REE: • Disease progression, pulmonary function, fat free mass (FFM), pancreatic status, gender, age, pubertal status and exercise. Also lack of consistency in findings with somewhat conflicting results in the following areas: • Correlation between REE and FFM, pancreatic function and pulmonary function. • Change in REE with acute respiratory exacerbations. • Impact of gender and puberty on REE.
Clinical impact	**D** Poor	Due to conflicting results, the clinical impact is difficult to assess. Despite some evidence of altered REE for people with CF, guidance is lacking in regards to the practical application of these findings. • Individual variation in energy requirements aren't accounted for. • Unable to use results to guide best practice when estimating energy requirements and setting energy targets for people with CF.
Generalisability	**D** Poor	Most studies in children only (few studies include adults).
Applicability	**C** Satisfactory	Applicable to the Australian & NZ environment

Chapter 7 Q7.1.2 Are protein requirements increased in the CF population compared to the general population?
No evidence available

Chapter 7 Q7.1.3 What is the evidence to support the routine recommendation of a high fat diet for people with CF?
NHMRC Grade for recommendation: Grade D
Evidence statement: There were no new studies included in this systematic literature review (2002-2016) to make changes to the existing recommendation for fat intake in CF. The *Australasian CF Guidelines (2006)* recommended an unrestricted diet, containing adequate fat to meet energy requirements. Target 100g/day if over five years of age based on the premise that a diet high in fat is less bulky and more achievable than a diet that is low in fat. Studies published since 2002 focused on the lipid profile and supplementation of essential fatty acids in people with CF.

Chapter 7 Q7.1.4 What are the recommendations for fibre in people with CF?
No evidence available

7.2 Essential Fatty Acids

Chapter 7 Q7.2.1 Does dietary supplementation with omega-3 essential fatty acids improve health outcomes in people with CF?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: There is some evidence to suggest that dietary supplementation with omega 3 fatty acids may improve health outcomes for people with CF; this evidence relates only to 'biochemical' health outcomes and not to 'clinical' or 'therapeutic' health outcomes. There is insufficient evidence to recommend routine omega-3 fatty acid supplementation for improving health outcomes in either children or adults with CF and there is no evidence to recommend routine omega-3 fatty acid supplementation for improving health outcomes in infants with CF. There is insufficient evidence to suggest that any one particular type of omega-3 fatty acid or a mix of omega-3 fatty acids is superior for improving health outcomes in people with CF.		
Evidence base	**D** Poor	3 studies included: • 1 level 1 randomised control study, n= 20 children and young adults • 1 level III-3 study (n= quality) • 1 level IV study (n= quality)
Consistency	**D** Poor	Studies looked at a variety of outcomes and were difficult to compare for consistency. • Fatty acid content of membrane phospholipids - findings consistently demonstrate increased omega-3 content of membrane phospholipids post omega-3 supplementation. • FEV_1 - inconsistent findings. • Nutritional status - inconsistent findings. • Inflammatory markers - findings consistently demonstrate an anti-inflammatory effect of omega-3 supplementation. • Antibiotic use – inconsistent findings. For all health outcomes in this review the evidence is inconsistent in terms of specific type of omega 3 fatty acid used as a supplement, dose and duration of supplementation required to achieve the effect.
Clinical impact	**D** Poor	Difficult to ascertain the clinical impact due to the following: • Dose and duration required to achieve the effect is inconclusive. • Size of the effect was unable to be measured due to underpowered sample sizes. • Many studies failed to report on adverse events.
Generalisability	**B** Good	Given the heterogeneous nature of CF and the fact that overall the studies address this heterogeneity, it is clinically sensible to apply the above evidence to the target CF population.
Applicability	**B** Good	Omega-3 supplements are available on the Australian and New Zealand market however compliance may be an issue in the CF population.

Chapter 8 **Fat Soluble Vitamins**

8.1 Vitamin A

Chapter 8 Q 8.1.1 How should vitamin A be assessed for people with CF?
No evidence available

Chapter 8 Q8.1.2 What is the role for routine supplementation of vitamin A in people with CF and pancreatic insufficiency?		
NHMRC Grade for recommendation: Grade D		
Evidence statement: The evidence is unclear regarding the need for routine versus individualised supplementation of Vitamin A in people with CF. Whilst some studies suggest that routine supplementation is required, others suggest that not all people with CF and pancreatic insufficiency require supplements and that supplementation should be individualised based on serum levels. There is no evidence to suggest a need to change from current practice.		
Evidence base	**C** Satisfactory	The vitamin A evidence base is primarily for supplementation of vitamin A as retinol or retinol/ β-carotene combination. There is a small body of evidence for the adjunctive supplementation of β-carotene as an anti-oxidant. **Retinol** 2 level II studies • Children n=46 children, positive quality • Children & adolescents n=22, negative quality 2 level III studies • Infants n=39; positive quality • Children & Adults: n=138; neutral quality 11 level IV studies (10/11 studies neutral quality, 1/8 studies positive quality) • Children n=73, n=70, n=41, n=556 • Children & Adults n=32, n=78, n=98, n=221, n=102 • Infants, children & adults n=35 • Adults: n=43 β-carotene 1 level II study (n=46 CF children); positive quality 1 level IV study (n=17 children & adults); positive study
Consistency	**D** Poor	Difficulties in assessing the need for routine versus individualised supplementation of vitamin A due to lack of consistency between studies with the following: • Definitions used to define vitamin A status (inconsistent reported prevalence of vitamin A deficiency and excess). • Methods of assessment and reporting of dietary vitamin A intake, serum vitamin A reference ranges, supplementation formulation & doses. • Comparison study populations. Most studies unable to assess causation and can only provide suggestive or inferential evidence only. Some consistency in the following: • Australian studies do not suggest excessive intakes of vitamin A with current recommended levels of supplementation. • No association between serum levels of vitamin A and intake. Insufficient evidence to suggest routine supplementation with β-carotene. • Studies consistently report deficiency of β-carotene and improvement of β-carotene levels with supplementation. However there is limited and unclear evidence re the effects of β-carotene supplementation on clinical outcomes and they are likely reflective of the total antioxidant mixture rather than β-carotene in isolation.

Clinical impact	**C** Satisfactory	Evidence unclear regarding the association between improved retinol levels with supplementation and clinically important outcomes i.e. pulmonary status.

Generalisability	**C** Satisfactory	Most evidence is from children and adults, without CF-liver disease and with mild-moderate lung disease.
		• Over 60% of studies included both pancreatic insufficient and pancreatic sufficient patients.
		• Only 2 studies included infants.
		• Only 5 studies with Australian populations.
		  ○ High reported intakes of vitamin A have generally been reported in studies from the US.
		  ○ Vitamin A sources (dietary & supplements) and methods of assessment not always generalisable to Australian context.

Applicability	**C** Satisfactory	• Only one CF-specific multivitamin supplement is available in Australia/NZ and its formulation/composition has not changed since the 2006 guidelines. • Significant differences in food sources of vitamin A between countries. • No excessive vitamin A intakes reported in Australia/NZ studies. • β-carotene is not available as an individual prescription supplement in Australia/NZ and the available CF-specific multivitamin has only a low percentage as β-carotene. • Limited options for increasing Vitamin A supplementation where there is risk of toxicity from preformed retinol.

Chapter 8 Q8.1.3 What vitamin A supplementation dose should be prescribed to treat vitamin A deficiency in people with CF?

NHMRC Grade for recommendation: Grade D

Evidence statement: Evidence available from only one study suggesting supplementation of low serum retinol levels in infants of between 1500 – 2210 IU/day, which is in line with current 2006 recommendations. There is no evidence to guide practice in children (>12 months) or adults with CF.

Evidence base	**D** Poor	1 level III study, n=39 infants; positive quality
Consistency	N/A	-
Clinical impact	**C** Satisfactory	No evidence found to implicate vitamin A deficiency and the early development of CF lung disease, including airway inflammation, during infancy. Length of follow up (1 year) may be too short to see significant effects.
Generalisability	**C** Satisfactory	Generalisable only to infants. • 77% pancreatic insufficient. • All patients clinically stable
Applicability	**B** Good	Australian study

Chapter 8 Q8.1.4 What is the safe upper limit for vitamin A supplementation in people with CF?

No evidence available

Chapter 8 Q8.1.5 How often should vitamin A levels be measured in people with CF?

No evidence available

8.2 Vitamin D

Chapter 8 Q8.2.1 Is vitamin D status associated with measures of respiratory health (lung function, pulmonary exacerbations, markers of inflammation) in people with CF?		
NHMRC Grade for recommendation: Grade D		
Evidence statement There is an increasing interest in the potential association between vitamin D status and markers of pulmonary function. However within the area of CF, the evidence base remains small with significant limitations and the findings are inconsistent. Further research is required to establish if vitamin D status is a contributing factor to the clinical course of lung disease in CF rather than an association.		
Evidence base	**D** Poor	7 papers representing 6 studies – all of neutral quality. • One level II study - double blind, placebo controlled RCT (n=15 adults with CF and 15 controls). • One level III study - retrospective cohort (n=130 children). • Four level IV studies - retrospective cross sectional studies (n=898 children and adults; n =597 children and adults; n=148 children; n=53 children).
Consistency	**D** Poor	Lung function (FEV1) & vitamin D (5 studies). Inconsistent findings: • 2 level IV studies found a significant positive association between FEV1 and vitamin D status while the other 3 (2 level IV and 1 level III-2) found no significant association. Markers of Inflammation & vitamin D (3 studies). Inconsistent findings: • 1 level II study showed a significant reduction in TNFα but not in other inflammatory cytokines after giving a one off high dose of vitamin D. • 1 level IV study showed no association between vitamin D and IgG, IgE and CRP. • 1 level 1V study found a significant reduction in IgG with higher vitamin D levels. Pulmonary Exacerbations and vitamin D (2 studies): • Both low level and small in number have looked at vitamin D status and pulmonary exacerbations, no conclusions can be drawn from this. One level IV study showed that vitamin D status was an independent determinant of the number of pulmonary exacerbations. One level IV study showed that the rate of pulmonary exacerbations in those deficient in vitamin D between the ages 15-18yrs was significantly higher than those who were insufficient or sufficient within that age group.
Clinical impact	**D** Poor	Relevance of the evidence to the clinical question is poor. • FEV1 % predicted most commonly assessed measure • Findings are very inconsistent No evidence to support a causal link as the influence of other confounding variables was not assessed in most of the studies
Generalisability	**B** Good	The studies to date have been based in children and adults with CF from CF care centres worldwide which are comparable to Australasian CF centres.
Applicability	**B** Good	The findings of the studies to date would be relevant to Australasian CF populations

Chapter 8 Q 8.2.2 Is there an ideal serum 25-hydroxyvitamin D level to aim for in people with CF?
No evidence specific to CF available

Chapter 8 Q8.2.3 Is the time of year, specifically the season, important when measuring and interpreting an individual's serum vitamin D level?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: There is satisfactory evidence (from cross sectional studies) that vitamin D levels drawn in months of lower UVB exposure, regardless of latitude, are lower than those drawn in months of higher UVB exposure. Therefore the time of year is an important factor when interpreting an individual's serum vitamin D level. From this it could be extrapolated that achieving an adequate vitamin D status through the whole year is best achieved by measuring serum vitamin D at the end of winter and adjusting dosing regimens accordingly.		
Evidence Base	**C** Satisfactory	8 studies included in the body of evidence. • One level III study (case control); n=141 CF patients >1yr of age; negative quality. • Seven level IV studies (retrospective cross sectional studies). • 1 study; n=89 CF children; negative quality • 6 studies; neutral quality o n=556, n=129, n=148, n=290 children o n=597 adults and children o n=58 newborns
Consistency	**B** Good	The majority of studies, including the two largest studies (> 1000 people with CF), demonstrated that vitamin D levels drawn in months of higher UVB exposure are significantly greater than those in months of lower UVB exposure. Studies that showed no difference were smaller and potentially not powered adequately to show a seasonal difference.
Clinical Impact	**C** Satisfactory	Clinically relevant as the results provide guidance as to: • The best time of year to check vitamin D levels. • What to do in terms of supplementation based on your findings.
Generalisability	**B** Good	Studies acknowledged that an individual's total UVB exposure is dependent on how far they live from the equator. The further away you are the less exposure you receive. Studies acknowledged that UVB rays are stronger during the spring and summer months regardless of where you live. Despite the studies above being conducted in countries outside of Australasia, the findings can be generalised to apply to most countries. Mostly in children with only one study including adults.
Applicability	**C** Satisfactory	Application of findings i.e. testing vitamin D at the end of winter would be limited by several factors: • Variation in vitamin D measurements between laboratories means that use of one central laboratory is best practice, but may not be feasible for all individuals. • Individuals often have bloods checked opportunistically e.g. as an inpatient or while under sedation for a procedure. CF clinics usually manage individuals from a large geographical region, including those from rural locations who may be unable to attend CF clinic at the end of winter for a blood test.

Chapter 8 Q8.2.4 Should supplemental vitamin D be given to all people with pancreatic sufficient cystic fibrosis as part of routine care?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: There have been numerous studies, mostly level IV (retrospective chart reviews) that have looked to describe vitamin D deficiency and sufficiency in people with CF (both pancreatic sufficient and insufficient). These studies have been conducted in different geographical locations, usually with small numbers of pancreatic sufficient people and poorly controlled for known risk factors for low serum vitamin D (including the time of year of testing). Therefore the literature does not provide a good evidence base to answer whether routine vitamin D supplementation should be given to all people with CF. It should be noted however that regardless of study design and country of origin these studies have shown that it is a common finding for pancreatic sufficient people with CF to be deficient in vitamin D.		

Evidence Base	**C** Satisfactory	8 studies included in the body of evidence:
		• One level III retrospective cohort study; n=360 adults; neutral
		• 7 level IV cross sectional chart reviews; all of neutral quality
		  ○ n=58 infants
		  ○ n=556, n=290, n=129, n=148, n=77 children
		  ○ n=297 children and adults

Consistency	**D** Poor	Inconsistent findings relating to pancreatic status and serum vitamin D levels. Some report the percentage of pancreatic sufficient and pancreatic insufficient people who fall below set vitamin D level. Cut off vitamin D level varies between studies. No universally accepted definition of vitamin D deficiency. Some studies report mean or median vitamin D levels. The number of pancreatic sufficient people is usually low and not always adequately powered to detect a difference. All but one study did not match for other potential confounders e.g. season of testing, gender and age. Of the eight studies reviewed: • 5 studies found no significant difference in vitamin D status between pancreatic sufficient and insufficient patients • 3 studies found a significant difference in vitamin D status between pancreatic sufficient and insufficient patients (1 showing that mean serum levels were significantly lower in pancreatic insufficient patients and 2 showing that those who were pancreatic insufficient were significantly more likely to be deficient (based on a cut off of 25nmol/L).
Clinical Impact	**C** Satisfactory	The finding that pancreatic sufficient individuals are at risk of vitamin D deficiency is important in guiding clinical practise: • Highlights that annual screening is important for everyone • There may be a potential role in routine supplementation for all people with CF
Generalisability	**C** Satisfactory	Studies mostly conducted in children. Each clinic likely differed in their approach to routine supplementation of those with pancreatic sufficiency. Individuals from different countries were likely to have received varying amount of UVB exposure as well as different amounts of vitamin D from food (some countries having mandatory fortification and others not). Overall somewhat generalizable to the Australian community.
Applicability	**B** Good	It is feasible to expect that all individuals with CF and not just those who are pancreatic insufficient, undergo annual serum vitamin D testing and supplementation as needed

Chapter 8 Q 8.2.5 What doses of vitamin D are needed to prevent deficiency in people with CF?
No evidence available

Chapter 8 Q8.2.6 What doses of vitamin D are needed to correct deficiency in people with CF?		
NHMRC Grade for recommendation: **Grade C**		
Evidence statement: Whilst there is good evidence in the use of high dose cholecalciferol to correct deficiency in people with CF, there is limited benefit in its application to the Australian and NZ setting given our knowledge of potential toxicity in some people who may be unable to convert excess cholecalciferol to its inactive form. There is a lack of evidence on conventional, daily doses of vitamin D needed to correct vitamin D deficiency. In the absence of CF-specific doses needed to correct deficiency, guidance should be taken from the general Australian and NZ population recommendations as well as recommendations from other CF-specific guidelines.		
Evidence Base	**B** Good	2 studies looked at a set dosing protocol and measured subsequent serum vitamin D levels. • 1 level II intervention, positive quality (50 000IU vitamin D) study; n=30 adolescents and adults. • 1 level III intervention, neutral quality (100 000-600 000IU); n=38 children. Other studies have reported the general practice of their clinic in terms of supplementation and then described mean vitamin D levels. These studies were not included as they lacked an assessment of individual doses and adherence.
Consistency	**B** Good	Consistent findings that high dose cholecalciferol can significantly raise serum vitamin D levels in individuals with CF.
Clinical Impact	**D** Poor	There is benefit in using high dose cholecalciferol to correct vitamin D deficiency in people with CF. Given the risk versus benefit of using high dose supplementation (due to potential toxicity), the potential benefit from applying this protocol is poor.
Generalisability	**B** Good	The findings of these studies can be applied to the Australian and New Zealand setting.
Applicability	**D** Poor	Evidence of an autosomal recessive mutation which can affect the conversion of excess cholecalciferol to its inactive form therefore increasing the risk of hypercalcaemia. • Some hospitals have advised against the use of high dose treatment i.e. 50,000IU • There is a lack of studies that are based on the more conventional, daily dosing of vitamin D which would be more applicable to Australian and NZ CF centres.

8.3 Vitamin E

Chapter 8 Q8.3.1 How should vitamin E levels be assessed for people with CF?
No evidence available

Chapter 8 Q8.3.2 What is the role for supplementation of vitamin E in people with CF?
NHMRC Grade for recommendation: Grade C
Evidence statement: The evidence suggests the need for routine supplementation of vitamin E in all pancreatic insufficient people with CF. There is inadequate evidence to establish recommendations for a supplement dose.

Evidence base	**C** Satisfactory	14 studies included in body of evidence: 2 level II studies • Children: n=46; positive quality • Children & adolescents: n=22; negative quality 3 level III studies; positive quality • Infants: n=39, n=71 • Children: n=232 8 level IV studies; neutral quality • Infants, children & adults: n=35 • Children: n=69, n=70, n=556 • Children & adults: n=102, n=10 • Adults: n=93, n=43 1 level IV study; positive quality • Children & adults: n=17
Consistency	**C** Satisfactory	Studies mostly consistent in suggesting need for routine supplementation of vitamin E however variability between studies in the following areas: • Definition of vitamin E adequacy (no clear reference range or target for supplementation). • Dietary intake of vitamin E. • Association between vitamin E intake and α-tocopherol levels. Most studies supplemented at levels within CF consensus guideline recommended ranges with inconsistent evidence of efficacy of these doses on serum levels and clinical outcomes. Most studies suggest that supplement intake below CF recommended guidelines is most likely inadequate. There is limited and unclear evidence regarding need for routine supplementation in pancreatic sufficient patients.
Clinical impact	**C** Satisfactory	Implementation likely to impact CF population: • Vitamin E supplementation is effective in increasing serum levels of α-tocopherol. • Vitamin E deficiency is still common though there is some limited evidence of high levels though not in Australian/NZ populations. • Limited and unclear evidence correlating improved vitamin E levels post supplementation and important clinical outcomes such as pulmonary function, improved oxidative stress and cognitive status.
Generalisability	**C** Satisfactory	Most evidence from children and adults with no CF-related liver disease and mild-moderate lung disease. • Only 3 studies with infants. • Over 70% of studies included both pancreatic insufficient and insufficient patients. • Evidence not generalisable to those with more severe lung disease.
Applicability	**C** Satisfactory	Only 3 studies with Australian populations Only one CF-specific multivitamin available in Australia/NZ and its composition has not changed since last guidelines. Greater variability in choice of supplement formulations in settings outside of Australia/NZ however with vitamin E content similar to the formulation available in Australia. No high vitamin E intakes have been shown in Australian/NZ studies.

Chapter 8 Q 8.3.3 What is the safe upper limit for vitamin E supplementation in people with CF?
No evidence available

Chapter 8 Q 8.3.4 How often should vitamin E levels be measured in people with CF?
No evidence available

8.4 Vitamin K

Chapter 8 Q 8.4.1 How should vitamin K status be assessed for people with CF?
No evidence available

Chapter 8 Q8.4.2 Should vitamin K supplementation be recommended for all people with CF and pancreatic insufficiency?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: The evidence suggests that vitamin K supplementation is required for all people with CF and pancreatic insufficiency. There is insufficient high quality evidence available to recommend an optimal dose. Given the recent evidence suggesting the importance of vitamin K in bone health, it is recommended where possible, that practitioners follow the recommendations of the most recent guidelines. In practice this will require an increase in vitamin K supplementation doses that are routinely provided and currently available in Australia.		
Evidence base	**D** Poor	Nine studies included in evidence base: 1 level II intervention study; neutral quality n=14; children 1 level III-3 diagnostic case-control study; neutral quality; n=32; infants, children & young adults 7 level IV studies • 1 prospective, non-randomised trial; positive quality; n=17; children • 1 diagnostic study; negative quality; n=20; children • 5 aetiology studies; 4 positive quality; n=97; children & adults; n=81, 32, 20; children; 1 neutral quality; n=106; children
Consistency	**B** Good	Generally studies consistently report the following: • Suboptimal levels of vitamin K as assessed by PIVKA-II and uc-OC%. • Increased likelihood of inadequate vitamin K status with low level supplementation (<500ug/d). Overall studies are consistent in showing lower levels of bone formation markers in CF compared with healthy controls. • Inconsistent as to the effect of vitamin K supplementation on bone turnover markers. Evidence consistently shows no association between vitamin K status and bone mineral density.
Clinical impact	**C** Satisfactory	Evidence suggests the following: • Adequate vitamin K supplementation will decrease the incidence of subclinical vitamin K deficiency. • Subclinical deficiency of vitamin K may negatively impact the bone health of people with CF. • Vitamin K supplementation appears to be safe at doses significantly higher than current supplementation practices in Australia

Generalisability	**C** Satisfactory	Most evidence is from children and adults, mostly without CF-related liver disease, with pancreatic insufficiency, mild to moderate lung disease and variable nutritional status. The evidence can generally be applied across a heterogeneous CF population, however is less generalisable to infants and to people with CF and pancreatic sufficient or with CF-related liver disease.
Applicability	**C** Satisfactory	The only CF fat soluble multivitamin available in Australia (VitABDECK) provides 150ug per capsule of Vitamin K • Less than supplementation doses associated with more optimal vitamin K status • Vitamin K as an individual supplement is not readily available in most clinics. • The need for an additional vitamin K supplement would incur an additional cost and add to patient treatment burden.

Chapter 8 Q 8.4.3 How often should vitamin K levels be measured in people with CF?
No evidence available

Chapter 9 **Minerals**

9.1 Iron

Chapter 9 Q9.1.1 How should iron status be assessed in people with CF?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: Soluble transferrin receptor (sTfR) is unaffected by the acute phase response and may be a useful biomarker to measure when assessing iron status for people with CF. However, the overall body of evidence to guide practice for assessing iron status in CF is insufficient. Further research or expert consensus is required. Until further evidence is available, it is suggested that iron status in CF be assessed as per recommendations for the general population.		
Evidence base	**C** Satisfactory	Two diagnostic studies • One level III-2 study (n=70 adolescent and adult CF patients; ADA neutral) • One level III-2 study (n=127 adult CF patients; ADA positive)
Consistency	**C** Satisfactory	Both studies concluded that soluble transferrin receptor (sTfR) was a useful biomarker to help assess iron status in CF as it is not affected by the acute phase response with inflammation. Inconsistency between the studies regarding the use of serum ferritin in diagnosing iron deficiency in CF. • Study 1 found no correlation between serum ferritin and CRP • Study 2 found a significant correlation between ferritin and CRP
Clinical impact	**B** Good	Relevance of the evidence to the clinical question is satisfactory.
Generalisability	**B** Good	No paediatric patients under the age of 16 were included in either study. Evidence to support the assessment of iron status in the paediatric population is lacking.
Applicability	**B** Good	The measure of sTfR may not be available to all patients with CF. The cost of measuring sTfR may limit access to this biochemical measure at some facilities.

Chapter 9 Q9.1.2 How should iron deficiency be treated in people with CF?
No evidence available

Chapter 9 Q9.1.3 Is iron supplementation contraindicated in people with CF who are chronically colonised with Pseudomonas aeruginosa?		
NHMRC Grade for recommendation: Grade D		
Evidence statement: There is insufficient evidence from clinical trials to suggest that iron supplementation is contraindicated in adults and children with CF who are chronically colonised with Pseudomonas aeruginosa (PA). When indicated, an iron supplement should be prescribed for adults and children with CF who are chronically colonised with PA.		
Evidence base	**D** Poor	One randomized double blind placebo controlled crossover trial to answer this PICO. • Level II study (n=22 CF adults; ADA positive)
Consistency	N/A	
Clinical impact	**D** Poor	No adverse effect on sputum microbiome or pulmonary exacerbation score but the study was underpowered to detect a significant difference
Generalisability	**B** Good	All adults (no paediatric patients). Mostly males
Applicability	**B** Good	Applicable to the Australia CF population

9.2 Magnesium

Chapter 9 Q9.2.1 Does supplementing magnesium above the RDI improve nutrition and/or respiratory outcomes in people with CF?		
NHMRC Grade for recommendation: Grade D		
Evidence statement: There is insufficient evidence to support the suggestion that magnesium supplementation improves respiratory outcomes in CF. No studies have looked at magnesium supplementation and nutrition outcomes in CF.		
Evidence base	**D** Poor	One study only – double blind, randomized placebo controlled cross-over study • Level II study (n=44 paediatric patients; ADA positive)
Consistency	N/A	
Clinical impact	**C** Satisfactory	Relevance of the evidence to the clinical question is satisfactory.
Generalisability	**D** Poor	• Paediatric patients only • Majority of population was pancreatic sufficient • Mean FEV1 75% predicted which is much lower than the Australian paediatric population.
Applicability	**D** Poor	Population group studied not applicable to the Australian and NZ context .

9.3 Calcium

Refer to **Chapter 13** Bone Health for all relevant calcium content.

9.4 Sodium

Chapter 9 Q9.4.1 How do environmental factors and exercise impact on sodium requirements for people with CF compared to those without CF?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: There is insufficient evidence available to determine how environmental factor and exercise impact on sodium requirements for people with CF. The available evidence is from small, underpowered studies and is unable to be used to recommend sodium supplementation for the CF population.		
Evidence base	**D** Poor	3 small and underpowered studies • Level II study (n=11 CF patients aged 11-20 years; ADA positive) • Level III study (n=21 CF adults, ADA positive) • One level IV (n=20 infants; ADA neutral)
Consistency	**C** Satisfactory	The level IV study provided a general recommendation for sodium supplementation for CF infants in a hot/humid climate The level IV and II study identify serum sodium (hyponatraemia) as an insensitive marker of dehydration The level II and III study identify perceived thirst and thirst drive to be altered in CF
Clinical impact	**C** Satisfactory	The clinical impact is difficult to assess with small and underpowered studies. Safety of high dose sodium supplementation was not assessed.
Generalisability	**C** Satisfactory	Each study looked at a different age group; infants (0-12 months), children & adolescents (11-20 years) and adults (18 years +). • Numbers in each study were small. • No study included young children aged 1-10 years.
Applicability	**C** Good	Climate difference exists between the studies based on location or geography. Not always applicable to the Australian context

Chapter 9 Q9.4.2 What is the recommended daily sodium requirement for people with CF compared to those without CF?		
NHMRC Grade for recommendation: Grade D		
Evidence statement: There are no randomised control trials and insufficient evidence available to provide specific sodium supplementation doses for people with CF. The evidence refers only to infants; there is no evidence to guide sodium supplementation for the broader paediatric and adult CF population.		
Evidence base	**D** Poor	One small observational case study • Level IV study (n=10 infants, ADA negative)
Consistency	N/A	-
Clinical impact	**D** Poor	The findings are unlikely to alter current clinical practice.
Generalisability	**D** Poor	CF infants only. Small study size. No pancreatic sufficient patients included in the study
Applicability	**B** Good	The study was conducted in a country with an established health-care system similar to that of Australia

9.5 Zinc

Chapter 9 Q9.5.1 How should zinc status be assessed for people with CF?		
NHMRC Grade for recommendation: Grade D		
Evidence statement: There are no diagnostic studies addressing this question. Plasma zinc is the most common measure used to assess zinc status.		
Evidence base	**D** Poor	Only one study includes two measures of assessing zinc status. • Level IV cross sectional (n=53 people, neutral quality)
Consistency	N/A	-
Clinical impact	**D** Poor	Not a diagnostic study so unlikely to change clinical practice.
Generalisability	**C** Satisfactory	Includes diverse age group, all pancreatic insufficient.
Applicability	**D** Poor	Red blood cell zinc test not routinely performed in practice. Limited evidence of its use in people with CF.

Chapter 9 Q9.5.2 What are the recommendations for zinc supplementation in people with CF?		
NHMRC Grade for recommendation: Grade D		
Evidence statement: There is inadequate evidence to assess the need for routine supplementation of zinc in people with CF. There is also inadequate evidence to establish recommendations for the supplement dose required to correct suspected zinc deficiency in CF.		

Evidence base	**C** Satisfactory	The evidence from each of the following studies indirectly addresses the PICO.
		4 intervention studies
		• 2 Level II studies
		  • n=40 CF children, positive quality
		  • n=26 CF children & adolescents, neutral quality
		• 2 Level IV studies
		  ○ n= 21 CF children, neutral quality
		  ○ n= 30 CF children, negative quality
		• 4 level cross-sectional studies
		• 4 Level IV studies
		  ○ n=62 children, positive quality
		  ○ n=101 children, neutral quality
		  ○ n= 53 children and adults, neutral quality
		  ○ n=304 adults, positive quality

Consistency	**D** Poor	Inconsistent relationships between deficient/suboptimal zinc status and clinical outcomes (nutritional, pulmonary, infection). Variable evidence of the effects of zinc supplementation on functional outcomes. Inconsistencies in evidence complicated by the variations in the cutoffs used to define zinc status; measures used to assess adequacy of diet intake; in the type, amount and frequency of zinc supplementation; in the outcomes measured; and variability in the baseline prevalence of zinc deficiency.

Clinical impact	**D** Poor	Indirect evidence only. Intervention studies with small sample sizes and likely underpowered. Variability in the baseline prevalence of zinc deficiency made it difficult to detect consistent changes due to zinc supplementation.
Generalisability	**D** Poor	Studies mostly relevant to children. Only one study with data available for adults and no studies with available data for infants alone. No Australian/NZ studies. Two studies in predominantly malnourished populations and are poorly generalisable to Australian/NZ context. Mostly pancreatic insufficient patients, with mild-moderate lung function, without liver disease or diabetes and with variable nutrition status.
Applicability	**C** Satisfactory	Studies conducted mostly in the US and also in Belgium, Canada, India and Iran. Variations between countries in zinc bioavailability of dietary sources, the fortification of foods with zinc and the recommended dietary intakes. Differences in zinc supplements available and the type and amount of zinc included in CF and general multivitamin supplements.

Chapter 9 Q9.5.3 What is the safe upper limit for zinc supplementation in CF?
No evidence available

Chapter 10 **Pancreatic Insufficiency and PERT**

Chapter 10 Q10.1.1 Does gastric emptying rate impact PERT efficacy in people with CF?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: Limited evidence suggests that gastric emptying rate may have an impact on PERT efficacy in individuals with CF. Limited evidence suggests that those with fast gastric emptying may benefit from taking enzymes before a meal. This evidence refers to children only.		
Evidence base	**B** Good	Two randomised crossover studies with a small sample size • One level II study – randomised cross-over trial (n=18 children; ADA positive) • One level II study – double blind randomised placebo-controlled crossover study (n=10 children; ADA neutral)
Consistency	**B** Good	Relatively good consistency between studies. 2 randomised control trials showed correlation between gastric emptying time and lipase activity. • One study found that when PERT was taken after a meal, lipase activity as measured by a breath test was higher in those with normal versus fast gastric emptying. • One study found a negative correlation between gastric emptying time and improvements in lipase activity as measured by a breath test.
Clinical impact	**B** Good	Relevance of the evidence to the clinical question is satisfactory. Unlikely any risks to changing timing of enzymes based on gastric emptying rate.
Generalisability	**C** Satisfactory	Studies included children only.
Applicability	**B** Good	PERT is readily available in Australia and NZ although less preparations are available, when compared to the European and US market.

Chapter 10 Q10.1.2 Does the timing of PERT administration in relation to a meal impact PERT efficacy in people with CF?		
NHMRC Grade for recommendation: Grade D		
Evidence statement: Limited evidence suggests that PERT is equally effective in achieving normal lipase activity when taken before or after a meal in individuals with CF. Limited evidence suggests that changing PERT timing in relation to a meal on an individual basis may improve or normalise lipase activity in individuals with CF. This evidence refers to children only. Further research is required.		
Evidence base	**D** Poor	One level II randomised double blind cross-over trial (n=18 children; ADA positive)
Consistency	N/A	-
Clinical impact	**B** Good	Relevance of the evidence to the clinical question is satisfactory. Changing the timing of PERT is a practical application to a daily medication in CF.
Generalisability	**C** Satisfactory	Study included children only
Applicability	**B** Good	PERT is readily available in Australia and NZ although less preparations are available, when compared to the European and US market

Chapter 10 Q10.1.3 How should PERT be dosed for people with CF to support optimal fat absorption?		
NHMRC Grade for recommendation: Grade D		
Evidence statement: There is insufficient evidence to suggest specific doses of PERT to support optimal fat absorption in individuals with CF. Doses within current guidelines of <4000 IU lipase/g of fat and <2500 IU lipase/kg/meal have been shown to be safe and efficacious. There is insufficient evidence to suggest a maximum dose of PERT. Studies show, however, that doses <10 000 IU lipase/kg/day are safe as assessed by adverse events. In a small number of studies, this maximum dose has been exceeded in the short term with no reports of adverse events including fibrosing colonopathy. There is insufficient evidence to suggest whether dosing per gram of fat or per kg of body weight per meal is more efficacious. Both methods have been shown to be efficacious. There is insufficient evidence to suggest how PERT is best dosed to optimise efficacy in enteral feeding.		
Evidence base	**B** Good	19 studies • One level IV observational, non-interventional, single arm study (n=64; ADA neutral) • One level IV prospective cohort study (n=12; ADA neutral) • Four level IV prospective open label multicentre studies (n=214, n=40, n=23, n=18; ADA neutral) • Five level II double blind randomised placebo controlled two period crossover studies (n=31, n=16, n=21, n=34, n=47; ADA positive) • One level II quality placebo controlled PERT withdrawal study (n=49; ADA positive) • One level II quality randomised placebo controlled crossover study (n=31; ADA neutral) • One level II prospective randomised crossover study (n=18; ADA neutral) • One level II prospective randomised crossover study (n=39; ADA positive) • One level III-3 phase 2 randomised, investigator-blinded, parallel group pilot study (n=16; ADA positive) • One level II randomised, double blind, parallel dose ranging study (n=117; ADA positive) • One level III-2 retrospective observational study (n=14482; ADA positive) • One level IV retrospective cross sectional study (n=1215; ADA neutral)

Consistency	**D** Poor	Overall poor consistency between studies due to differences in study design with enzyme preparations use, doses provided, treatment duration and the age of patients. Despite this, a wide range of doses was consistently shown to be safe.
Clinical impact	**C** Satisfactory	Relevance of the evidence to the clinical questions is satisfactory. Longer term studies are required to fully address clinical impact of PERT dosing in CF.
Generalisability	**C** Satisfactory	Studies included adults and children, adults only or children only. Common exclusion criteria included patients with pancreatic sufficiency, intestinal resection, diabetes, treatment with acid suppression medication, medical history of DIOS
Applicability	**B** Good	PERT is readily available in Australia and NZ although less preparations are available, when compared to the European and US market.

Chapter 10 Q10.1.4 Is there evidence to support the use of acid suppression medication to improve PERT efficacy for people with CF?

NHMRC Grade for recommendation: Grade C

Evidence statement: There is inconsistent and limited evidence to support the use of acid suppression medication to improve PERT efficacy for people with CF. There is some evidence to suggest that omeprazole may decrease faecal fat loss; however this evidence is only in children.

Evidence base	**B** Good	Two crossover studies with small sample sizes. • One level II randomised cross-over sudy (n=15 children; ADA positive) • One level II double blind randomised placebo-controlled crossover study (n=12 children and 10 adults; ADA neutral
Consistency	**D** Poor	One study found no effect of acid suppression on fat absorption. One study found faecal fat loss significantly decreased with omeprazole treatment.
Clinical impact	**C** Satisfactory	Relevance of the evidence to the clinical question is satisfactory. Studies had a small sample size. Safety of acid suppression medication was not assessed.
Generalisability	**C** Satisfactory	Only 1 of 2 studies included adults.
Applicability	**A** Excellent	Acid suppression medication and PERT readily available on the Australian and NZ market.

Chapter 10 Q10.1.5 What are the risks and long-term health implications associated with phthalate exposure via PERT to people with CF?

No evidence available

Chapter 11 **Gastrointestinal complications**

11.1 Gastro-oesophageal Reflux

Chapter 11 Q11.1.1 What are the nutrition considerations for the management of gastro-oesophageal Reflux (GOR) in Cystic Fibrosis?		
NHMRC Grade for recommendation: Grade D		
Evidence statement There is insufficient evidence available regarding nutrition considerations for the management of GOR, specific to CF. Further research into the impact of dietary factors on GOR in CF is warranted.		
Evidence Base	**D** Poor	2 small studies looked at GOR in CF treated with Nissen fundoplication • Level IV Ø quality study, n = 48 in children and adults with uncontrolled GOR • Level IV Ø quality study, n = 25 in children 2 relatively small studies reviewed acid suppression treatments as a treatment for GOR in CF • One level II positive quality study, n =17 RCT feasibility study in adults with CF • One level IV positive quality study, n=201 in adults with CF
Consistency	**D** Poor	The fundoplication study results showed limited consistency- one study showed no significant change in BMI/weight 1 year post fundoplication, and the other showed a significant improvement in weight 2 years post-surgery. The acid suppression treatment studies showed no significant changes in BMI.
Clinical impact	**D** Poor	Relevance of the evidence to the clinical question is restricted.
Generalisability	**D** Poor	Both fundoplication studies include children from 1 year of age but only one study also included adults. Only the adult CF population (no paediatrics) were studied in regards to acid suppressions and GOR.
Applicability	**B** Good	The studies were conducted in countries with an established health-care system.

11.2 Distal Intestinal Obstruction Syndrome (DIOS) and Constipation

Chapter 11 Q11.2.1 What are the nutrition considerations for the prevention and management of Distal Intestinal Obstruction Syndrome (DIOS) in CF?		
NHMRC Grade for recommendation Grade C		
Evidence statement: There is some evidence to suggest that in Cystic Fibrosis, inadequate PERT, including poor adherence and under-dosing, is unlikely to play a role in DIOS. The impact of dietary intake, particularly inadequate fibre and fluid intake on DIOS is unclear. Overall there is inadequate evidence to determine the overall role of nutrition in the prevention and management of DIOS and care should be taken when considering the impact of diet on DIOS as the evidence base is small, limited to the European environment and limitations exist surrounding the dietary intake methodology employed. The impact of sodium intake on DIOS has not been accounted for.		
Evidence base	**C** Satisfactory	2 relatively small studies with a moderate risk of bias; 1 large multi-centre prospective longitudinal study with a low risk of bias • One level II observational prospective longitudinal (cohort) study (n=102 CF children and adults; ADA positive) • One level III-2 case control study (n=12 CF children and adults, n=36 control; ADA neutral) • One level IV cross sectional study (n=40 CF children and adults; ADA negative)

Consistency	**C** Satisfactory	The level II study found that insufficient PERT intake was not a pre-disposing factor for DIOS. Low fibre and fluid intake were frequently observed. The level III-2 study found no indication that nutritional factors (calories, fat, fibre & fluid) or PERT played a role in the occurrence of DIOS.. The level IV study found no relationship between fibre intake and DIOS.
Clinical impact	**C** Satisfactory	Relevance of the evidence to the clinical question is satisfactory however it is difficult to rule out the role of nutrition in DIOS prevention due to the limited number of studies and study limitations.
Generalisability	**B** Good	Given the heterogeneous nature of CF and the fact that overall the studies address this heterogeneity, it is clinically sensible to apply the above evidence to the target CF population.
Applicability	**C** Satisfactory	Australian climate is different to the European climate studied in the body of evidence. Therefore it is difficult to apply the impact of fluid intake and hydration on DIOS prevention. The impact of sodium intake on DIOS was not studied. Adequacy of fibre intake was compared to the US fibre recommendations which differ from those used in Australia. Additional PERT preparations are available in Europe that aren't available in Australia.

Chapter 11 Q11.2.2 What are the nutrition considerations for the prevention and management of constipation in CF?		
NHMRC Grade for recommendation Grade D		
Evidence statement: There is inadequate evidence to determine the impact of nutrition in the prevention and management of constipation in CF. While one study has found that sub-optimal fat absorption may contribute to constipation and that inadequate fluid and fibre intake don't, the evidence base is small and not applicable to the Australian context.		
Evidence base	**C** Satisfactory	One level III retrospective cohort study (n=214; n=107 constipations and n=107 controls; ADA neutral).
Consistency	N/A	-
Clinical impact	**D** Poor	Relevance of the evidence to the clinical question is satisfactory however it is difficult to assess overall clinical impact with only 1 study.
Generalisability	**B** Good	Given the heterogeneous nature of CF and the fact that the study addresses this heterogeneity, it is clinically sensible to apply the above evidence to the target CF population.
Applicability	**D** Poor	Australian climate is different to that in the Netherlands. Therefore it is difficult to apply the impact of fluid intake and hydration on the prevalence of constipation in CF. The impact of sodium intake and constipation in CF was not studied. Adequacy of fibre intake was compared to the local fibre recommendations that differ from those used in Australia. Fat absorption was measured via an annual 3 day faecal fat test which is not routinely completed in Australia. Only paediatric patients included in the study.

11.3 Colon Cancer Screening

Chapter 11 Q11.3.1 What are the nutrition considerations for colon cancer screening in CF?
No evidence available

11.4 Liver Considerations

Chapter 11 Q11.4.1 Should vitamin K supplementation be recommended for all people with CF-related liver disease?
No evidence available

Chapter 11 Q11.4.2 What are the requirements for effective supplementation in episodes of vitamin A deficiency in peoples with CF-related liver disease?
No evidence available

Chapter 12 **CF-Related Diabetes**

This chapter is a narrative of the CF nutrition considerations and management of CFRD.

No clinical questions and PICOs were identified for this chapter.

Chapter 13 **Bone Health**

Chapter 13 Q13.1.1 How and when should bone mineral content and density be assessed for people with CF?
No evidence available

Chapter 13 Q13.1.2 Is there an ideal serum 25-hydroxyvitamin D level to aim for with people with CF?
No evidence available

Chapter 13 Q13.1.3 What are the calcium requirements in CF to reduce the risk of low bone mineral density?		
NHMRC Grade for recommendation Grade D		
Evidence statement: There is insufficient evidence available to provide specific calcium supplementation doses for people with CF. As a result, the calcium intake required to reduce the risk of low bone density in people with CF is unknown and in the absence of CF-specific data, calcium intake and supplementation should align with dietary reference intakes		
Evidence base	**D** Poor	One level II study • Randomised double blind placebo controlled trial investigating the effect of calcium and vitamin D supplementation on bone mineral density and bone metabolism in adult patients with cystic fibrosis (N=31 CF adults; neutral quality)
Consistency	N/A	-

Clinical impact	**D** Poor	Although calcium and vitamin D supplementation was found to reduce the rate of bone turnover and bone loss in adult CF patients, the results didn't reach statistical significance. Unable to assess overall clinical impact with one small study that includes adults with CF only.
Generalisability	**C** Satisfactory	Adult patients only
Applicability	**A** Excellent	Applicable to the Australian and New Zealand CF context.

Chapter 13 Q13.1.4 Does supplementating clacium above the RDI improve bone mineral density in people with CF?		
NHMRC Grade for recommendation Grade D		
Evidence statement: There is insufficient evidence to suggest that supplementing calcium above the RDI will improve bone mineral density in people with CF. If the RDI for calcium intake is unable to be met by diet, then calcium supplementation should be commenced.		
Evidence base	**D** Poor	One level II study • Double blinded randomised control trial (N=15 CF children; neutral quality)
Consistency	N/A	-
Clinical impact	**D** Poor	Relevance of the evidence to the clinical question is satisfactory however it is difficult to apply results to clinical practice due to the study limitations and small sample size studied (n=15).
Generalisability	**C** Satisfactory	Study group specific to CF however only paediatric patients were studied and the sample size was small (n=15) and mostly males (n=10/15).
Applicability	**A** Excellent	Applicable to the Australian and NZ CF context.

Chapter 14 **Special considerations for life stage and genotype**

14.1 Pregnancy

Chapter 14 Q14.1.1 What are the nutrition considerations of the management of pregnancy in CF?
No evidence available

Chapter 14 Q14.1.2 What recommendations around vitamin A supplementation and monitoring should be provided to women with CF who are pregnant or planning a pregnancy?
No evidence available

14.2 Genetic Modulator Therapies

Chapter 14 Q14.2.1 What are the implications of Ivacaftor on nutritional status in adults and children >2 years with CF who have at least one G551D or other gating mutation allele?		
Evidence statement: There is substantial high quality evidence that Ivacaftor improves nutritional outcomes, specifically weight and BMI, for adults and children >2 years with CF who have the G551D and other gating mutations. These findings appear to also be applicable to those with severe lung disease (i.e. awaiting transplantation or FEV1<40% predicted as evidenced by two level IV studies).		
Evidence base	**A** Excellent	5 Level II studies • All positive quality 3 level IV studies • All neutral quality • Includes a mixture of Phase II and III randomised control trials plus studies completed in post approval (real life) clinical settings
Consistency	**B** Good	Findings consistently demonstrate a significant improvement in weight and BMI post commencement of Ivacaftor in both children and adults. Whereas adult subjects with mild to moderate lung disease appear to have an acute weight gain (within a month) and then a plateau, paediatric subjects and those with severe lung disease show continuous weight gain over time – these differences appear repeatable and can be explained
Clinical impact	**A** Excellent	The improvements in weight and BMI seen are in-line with current recommendations for ideal nutritional status for people with CF.
Generalisability	**A** Excellent	Majority of studies completed in those with G551D but there is no reason to believe from current observational evidence that those with other gating mutations would behave differently. Almost all included studies were multi-centre and included Australian participants, it is therefore sensible to apply the above evidence to the Australian/NZ CF population who have at least one G551D or other gating mutation allele.
Applicability	**B** Good	Ivacaftor is currently available in Australia for children and adults > 6 years with G551D and other gating mutations via the pharmaceutical benefits scheme. Whilst this medication is approved for use in New Zealand, access can be difficult as the high cost of this medication is not subsidised.

Chapter 14 Q14.2.2 Are there any other nutritional considerations (energy, salt intake) that practitioners should take into consideration for people on Ivacaftor therapy?		
Evidence statement Studies consistently report weight gain, improvements in BMI and reduction in sweat chloride levels. Causes of weight gain associated with Ivacaftor therapy are likely to be multifactorial and have not yet been investigated in detail. Emerging data from one phase III RCT trail in children >6 years suggests that fat intake and absorption may be improved. Whilst there is substantial high quality evidence that Ivacaftor therapy significantly improves sweat chloride levels for individuals with the G551D allele and other gating mutations, the relationship between sodium intake and sweat chloride levels is currently unknown and requires further study.		
Evidence base	**D** Poor	A total of 8 studies that indirectly answer this PICO. • 5 Level II studies All positive quality • 4 level IV studies • 3 neutral quality , 1 negative quality
Consistency	**B** Good	Studies consistently report weight gain, improvements in BMI and reduction in sweat chloride levels.
Clinical impact	**C** Satisfactory	Lack of direct evidence to assess clinical impact.
Generalisability	N/A	-
Applicability	N/A	-

Chapter 14 Q14.2.3 What is role of gastrointestinal and/or other nutritional outcome measures in people with CF receiving Ivacaftor therapy?
No evidence available

Chapter 15 **Complementary Therapies**

15.1 Probiotics

Chapter 15 Q15.1.1 Does dietary supplementation with probiotic genus *Lactobacillus* improve nutritional and/or respiratory status in people with CF?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: There is some evidence to suggest that dietary supplementation with a *Lactobacillus* genus probiotic may improve gastrointestinal and respiratory health outcomes for individuals with CF. The evidence from low quality and underpowered studies suggests that supplementation of a *Lactobacillus* genus probiotic may decrease intestinal inflammation and reduce the incidence and/or risk of pulmonary exacerbations in children and adults with CF. There is no evidence showing improvements in nutritional outcomes including BMI. There is no evidence for probiotic supplementation in infants with CF. Care should be taken at this time when applying this evidence to clinical practice.		
Evidence base	**D** Poor	Six Level II RCTs (n=37, ADA neutral; n=47, ADA negative; n=61, ADA neutral; n=30, ADA neutral; n=38, ADA neutral; n=22, ADA neutral) One Level III-2 two phase case controlled study (n=30, ADA neutral) One Level IV case series (n=10, ADA neutral)
Consistency	**C** Satisfactory	Intestinal inflammation – findings consistently demonstrate significant reduction in faecal calprotectin post probiotics. Pulmonary exacerbations – findings consistently demonstrate significant reduction in the incidence and/or risk of pulmonary exacerbations post probiotics. FEV_1 – overall findings show no effect with regards to improvement of FEV_1 Nutritional – findings consistently show no significant changes to BMI with probiotics The studies were not consistent in the *Lactobacillus* species or strain used or the duration of supplementation making it difficult to compare outcomes and evidence of efficacy.
Clinical impact	**C** Satisfactory	Relevance of the evidence to the clinical question is satisfactory. Size of the effect difficult to determine due to underpowered studies. Likelihood of adverse events with *Lactobacillus* genera probiotic supplementation is low.
Generalisability	**B** Good	Given the heterogeneous nature of CF and the fact that overall the studies address this heterogeneity, it is clinically sensible to apply the above evidence to the target CF population in children and adults. There is no evidence for probiotic use in infants.
Applicability	**B** Good	*Lactobacillus* probiotic genera are available on the Australian and New Zealand market however they are expensive and not available on PBS. Compliance may be an issue in the CF population.

Chapter 15 Q15.1.2 Should routine or targeted use of probiotic supplements be recommended for people with CF?		
NHMRC Grade for recommendation: Grade C		
Evidence statement: There is some evidence to suggest that dietary supplementation with probiotics may improve health outcomes such as reducing intestinal inflammation and number of pulmonary exacerbations. This is evidence is underpowered and low quality. Studies are variable in the population studied, the health outcomes measured and the probiotic strain and duration of supplementation making it difficult to compare outcomes and evidence of efficacy. Care should be taken when applying this evidence in clinical practice.		
Evidence base	**D** Poor	Six Level II RCTs (n=37, ADA neutral; n=47, ADA negative; n=61, ADA neutral; n=30, ADA neutral; n=38, ADA neutral; n=22, ADA neutral) One Level III-2 two phase case controlled study (n=30, ADA neutral) One Level IV case series (n=10, ADA neutral)
Consistency	**C** Satisfactory	Intestinal inflammation – findings consistently demonstrate significant reduction in faecal calprotectin post probiotics. Pulmonary exacerbations – findings consistently demonstrate significant reduction in the incidence and/or risk of pulmonary exacerbations post probiotics. FEV_1 – overall findings show no effect with regards to improvement of FEV_1. Inflammatory markers – findings consistently demonstrate no improvement of inflammatory markers as measured by IL-8 and TNF-α post probiotics. The studies were not consistent in the probiotic species or strain used or the duration of supplementation making it difficult to compare outcomes and evidence of efficacy.
Clinical impact	**C** Satisfactory	Relevance of the evidence to the clinical question is satisfactory. Size of the effect difficult to determine due to underpowered studies. Likelihood of adverse events with probiotic supplementation is low.
Generalisability	**B** Good	Given the heterogeneous nature of CF and the fact that overall the studies address this heterogeneity, it is clinically sensible to apply the above evidence to the target CF population in children and adults. There is no evidence for probiotics in infants.
Applicability	**B** Good	Probiotics species and strains used in CF research, are available on the Australian and New Zealand market however they are expensive and not available on PBS. Compliance may be an issue in the CF population.

15.2 Glutathione

Chapter 15 Q15.2 Does antioxidant supplementation with oral glutathione or its precursor N-acetylcysteine improve nutritional and/or respiratory status in people with CF?
NHMRC Grade for recommendation Grade C
Evidence statement: There is some evidence to suggest that dietary supplementation with oral glutathione may improve nutritional outcomes, specifically weight and BMI, for individuals with CF. This evidence is inconsistent in terms of dose and duration of supplementation studied. There is conflicting evidence to suggest that dietary supplementation with oral glutathione or N-acetylcysteine improves respiratory outcomes. There is insufficient evidence to recommend either glutathione or N-acetylcysteine as having superiority for improving nutritional and/or respiratory status in individuals with CF and there is insufficient evidence to recommend a specific formulation, dose or duration required to achieve desirable nutritional and respiratory outcomes.

Evidence base	**C** Satisfactory	Three Level II RCTs (n=70, ADA positive; n=47, ADA neutral; n=43, ADA neutral) One Level III-2 non randomised comparative study (n=18, ADA negative) One Level IV case series study (n=13, ADA negative)
Consistency	**C** Satisfactory	FEV_1 – findings inconsistent with regards to the effect on FEV_1. Pulmonary exacerbations – studies inconsistent with regards to the effect on pulmonary exacerbations. Nutritional status – findings consistently demonstrate a significant improvement in weight and BMI post oral glutathione. Sputum neutrophils – findings inconsistent with regards to the effect on sputum neutrophils. Inflammatory markers - findings consistently demonstrate no significant improvement in inflammatory markers. Overall the evidence is inconsistent with regards to the study design, risk of bias, intervention studied and the dose and duration of intervention required to achieve the effect.
Clinical impact	**C** Satisfactory	Uncertain duration required to achieve the effect. Inability to determine the size of the effect due to underpowered studies. Unable to determine safety profile due to inconsistencies in the reporting of adverse events. Trend is towards a favourable safety profile. Relevance of the evidence to the clinical question is satisfactory.
Generalisability	**B** Good	Given the heterogeneous nature of CF and the fact that overall the studies address this heterogeneity, it is clinically sensible to apply the above evidence to the target CF population.
Applicability	**B** Good	Glutathione and N-acetylcysteine supplements are available on the Australian and New Zealand market however compliance may be an issue in the CF population.

15.3 Coconut Oil

Chapter 15 Q15.3 Is there evidence that dietary supplementation with coconut oil improves nutritional status in pancreatic insufficient people with CF?
No evidence available

15.4 Herbal Supplements

Chapter 15 Q15.4 Is there evidence that dietary supplementation with specific herbal products or their components improves health outcomes in individuals with CF?
NHMRC Grade for recommendation: Grade D

Evidence statement: There is no evidence that dietary supplementation with the specific herbal products garlic, curcumin or ginseng or their components improve health outcomes in individuals with CF. Garlic is the only herbal product that has been studied in humans with CF. The evidence relating to garlic supplementation for improving health outcomes in individuals with CF is minimal with only one trial demonstrating non-significant results for both respiratory and nutritional outcomes.		
Evidence base	**D** Poor	One Level II RCT (n=13, ADA neutral)
Consistency	N/A	N/A
Clinical impact	**D** Poor	Uncertain duration required to achieve the effect. Unable to determine the size of the effect.
Generalisability	**C** Satisfactory	It may be clinically sensible to apply this evidence to the CF population however uncertainties remain.
Applicability	**B** Good	Herbal supplements are available on the Australian and New Zealand market however compliance may be an issue in the CF population.

Chapter 16 **Lung Transplantation**

This chapter is a narrative of the CF nutrition considerations and management of lung transplantation.

No clinical questions and PICOs were identified for this chapter.

CHAPTER 19 APPENDICES

Appendix **A**

Cystic Fibrosis Role Statement

DAA Dietitians Association of Australia

Role Statement for Accredited Practising Dietitians practising in the area of Cystic Fibrosis

Developed by: Cystic Fibrosis Interest Group
Date Created: June 2014

Introduction

Accredited Practising Dietitians (APDs) are recognised professionals with the qualifications and skills to provide expert nutrition and dietary advice. APDs are qualified to advise individuals and groups on nutrition related matters.

APDs have sound university training accredited by DAA, undertake ongoing professional development and comply with the DAA guidelines for best practice. They are committed to the DAA Code of Professional Conduct and Statement of Ethical Practice, and to providing quality service.

APD is the only national credential recognised by the Australian Government, Medicare, the Department of Veterans Affairs and most private health funds as the quality standard for nutrition and dietetics services in Australia. It is a recognised trademark protected by law.

Purpose of this Role Statement

- To define the role an APD may fulfil when working in the area of Cystic Fibrosis (CF)
- To promote the knowledge and expertise of an APD, broadly and in the area of CF
- To advocate for dietetic services

Knowledge and skills in this area of practice

Entry level dietetic competencies ensure all APDs can conduct comprehensive assessments (assessment, diagnosis, intervention, monitoring and evaluation). Within a particular practice area, APD skills and knowledge will range from entry level to highly skilled. Within this continuum APDs can either fully manage the patient, seek support (clinical supervision, secondary consultation, mentor) to continue seeing the patient or choose to refer the patient on.
The following list of skills and knowledge required to work in CF are:

Skills:

- *Interpretation of markers of nutritional status* including: regular anthropometric and body compositional measurements, dietary intake measures, biochemical indices and medical screening procedures (e.g. DEXA scans, oral glucose tolerance tests.) [2]
- *Ability to provide advice tailored to the individual with CF, considering changing physiological needs, psychological barriers to optimal intake and life stage (e.g. adolescence, pregnancy, transplantation.)* [2]
- *Capacity to utilise chronic condition management approaches (e.g. partnering with individuals with CF and their caregivers, goal setting, reflective listening and questioning, motivational interviewing.)* [3-4]
- *Critical and clinical reasoning.*

Knowledge:

- *Thorough understanding of the role nutrition has in improving outcomes including longevity and quality-of-life for individuals with CF.* [5-6]
- *Familiarity with the pathophysiology of CF (e.g. effects on gut function, absorption, digestion, airways etc.), interdisciplinary management, and nutritional co-morbidities (i.e. CF related – diabetes, liver disease and bone disease.)* [1-2]

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Cystic Fibrosis Role Statement

- *Specific knowledge about pancreatic enzyme replacement therapy (i.e. preparations available, mechanisms of action, the link between food intake and dosing principles.)*

Activities entry level APDs would conduct:

- *Nutrition assessment skills.* Determine a CF patient's individual energy, salt and fluid needs, based on factors such as lung function, pancreatic function, nutritional co-morbidities, anthropometric and body compositional measurements, growth history, biochemical indices (e.g. fat soluble vitamin levels) and physical activity. [2]
- *Counselling and intervention*
- Determine realistic goals for nutritional therapy in collaboration with the patient and care-givers and other members of the CF team. [2]
- Provide comprehensive advice to assist in maintaining a healthy weight and in the management of other factors of CF, including: supplemental oral and enteral feeding (i.e. initiation, goal setting and monitoring), pancreatic insufficiency, fat soluble vitamin status, altered gastric motility, constipation and distal intestinal obstructive syndrome, CF related liver disease, impaired glucose tolerance/diabetes, reduced bone mineral density. [2]
- *Monitoring and evaluation*
- Conduct regular nutritional surveillance, with all aspects of nutrition and gastrointestinal status being reviewed. [1,2]
- *Effective communication skills*
- Communicate nutritional aspects of care with the individual with CF, their care-givers and the CF team to ensure continuity of care. [1,2]

Activities APDs working at a higher level would conduct:

- *Overseeing CF nutritional care of inpatients and outpatients, especially complex cases (i.e. transplantation, end-stage lung disease, intensive care setting, and enteral feeding.)* [1-2]
- *Management of home enteral nutrition service for CF patients, including gastrostomy tube monitoring and trouble shooting.*
- *Act as a nutrition resource person for the training, education and development and support of others involved in CF care. This includes the mentoring/supervision of students or less experienced dietitians as well as various other health professionals.* [1-2]
- *Lead or participate in nutrition and multi-professional quality improvement activities, research projects and/or audits.* [1-2]
- *Remain current with CF literature and practices by being a member of the CF Interest Group and other relevant international professional groups; undertaking professional development activities in the area of CF albeit internal or external (i.e. journal clubs, regular attendance at national or international meetings, presenting at professional and consumer forums on nutrition).*
- *Involvement in strategic and collaborative CF Interest Group activities.*

Any individual practitioner should refer to the Scope of Practice Decision Tool to determine if a task is within their scope of practice.

Activities APDs working in this area do not usually undertake:

- Sole nutritional management of patients, without the support of an interdisciplinary team from a recognised specialist CF centre (contact Cystic Fibrosis Australia for CF centre details.)
- Practicing in the CF area without engaging in ongoing professional development to build on knowledge and skills and without clinical supervision/mentoring.
- Providing psychological counselling outside of their skill-base.
- Prescribing pancreatic enzyme replacement therapy and ordering nutrition related biochemical tests (potential extended scope of dietetic practice in the future).

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Cystic Fibrosis Role Statement

Review date: June 2017

Appendix 1 – Background

The role of nutrition in CF care

Poor nutritional status is an independent risk factor for poor survival and has been associated with worse pulmonary function and other complications of CF, including bone disease. [2, 5-6]

Outcomes of APD involvement

- In a series of practice surveys from 1998 to 2010, the CF Interest Group has shown increasing alignment with dietetic practice standards (e.g. screening for CF related diabetes, completion of annual dietetic reviews, fat soluble vitamin screening and supplementation.) These surveys were not designed to review patient outcomes. [7-9]
- To begin evaluating the effectiveness of collaborative quality improvement and research activities undertaken by the CF Interest Group, a retrospective cohort study was performed on all individuals registered with the Australian Cystic Fibrosis Data Registry between 1999 and 2012 (n=85,363 yearly records). Body mass index (BMI) was used as a proxy for nutritional outcomes. The number of abstracts submitted to Australasian Cystic Fibrosis Conferences by dietitians was monitored also. Significant improvements in BMI were seen for children (aged 2-17 years, 1999 mean 47thBMI percentile vs 2012 mean 59th BMI percentile, p=0.0001) and adults (aged >18 years, 1999 mean BMI 21.3kg/m^2 vs 2012 mean BMI 23.0kg/m^2, p=0.0001.) Conference abstracts submitted increased exponentially (2 abstracts 1999 vs 26 abstracts 2013.) While it is not possible to delineate the impact of multidisciplinary team management, treatment changes and identification of milder CF genotypes; our data provides support that as health metrics go up – so too does APD 'presence'. [10]

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Link to entry level competencies

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Appendix **B**

Comparison of World Health Organisation and Centers for Disease Control and Prevention growth chart weight-for-age measurements in children birth to 24 months

This content has been adapted from https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5909a1.htm

The World Health Organization (WHO) released new international growth charts for children aged 0--59 months in 2006. These charts describe weight for age, length (or stature) for age, weight for length (or stature), and body mass index for age.

The US Centers for Disease Control and Prevention (CDC) charts describing how certain children grew in a particular place and time and are considered a growth reference. In contrast, the WHO charts describing the growth of healthy, predominately breastfed children in optimal conditions and are therefore considered a growth standard.

The CDC and NHMRC recommend that the 2006 WHO international growth charts are used for children from birth-24 months instead of the CDC growth charts. The CDC growth charts should continue to be used for individuals 2- 18 years of age in Australia and NZ WHO charts in New Zealand.

Clinicians should be aware that the WHO charts show a faster rate of weight gain in the first few months (figures 1 and 2) and therefore fewer children will be identified as underweight using the WHO charts. Beginning at approximately 3 months, the WHO charts show a slower rate of weight gain (figures 1 and 2), which is normal among breastfed infants from 3-18 months. Gaining weight more rapidly than indicated on the WHO charts may be early signs of overweight.

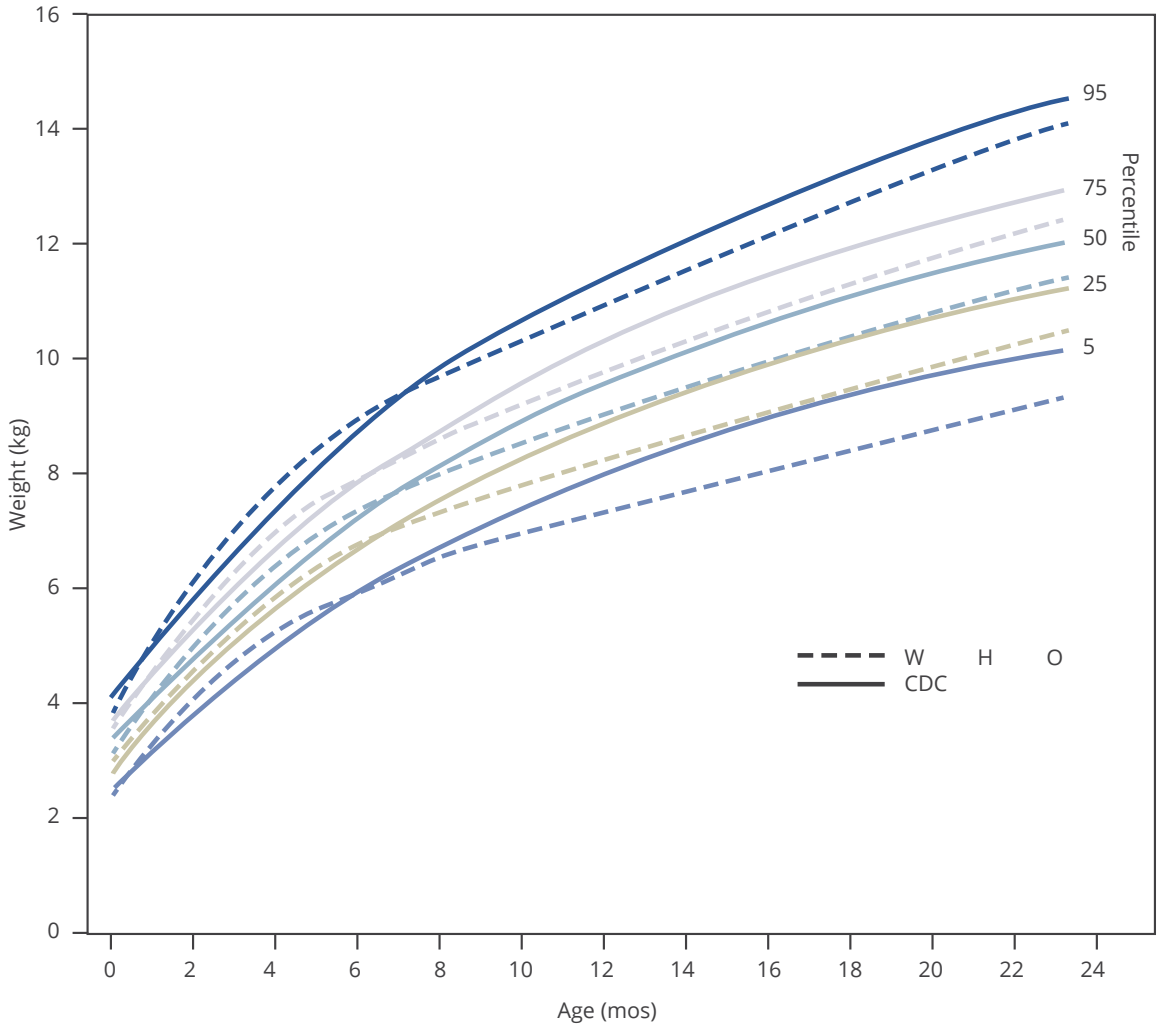

Figure 1- Comparison of World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) growth chart weight-for-age measurements for girls aged <24 months

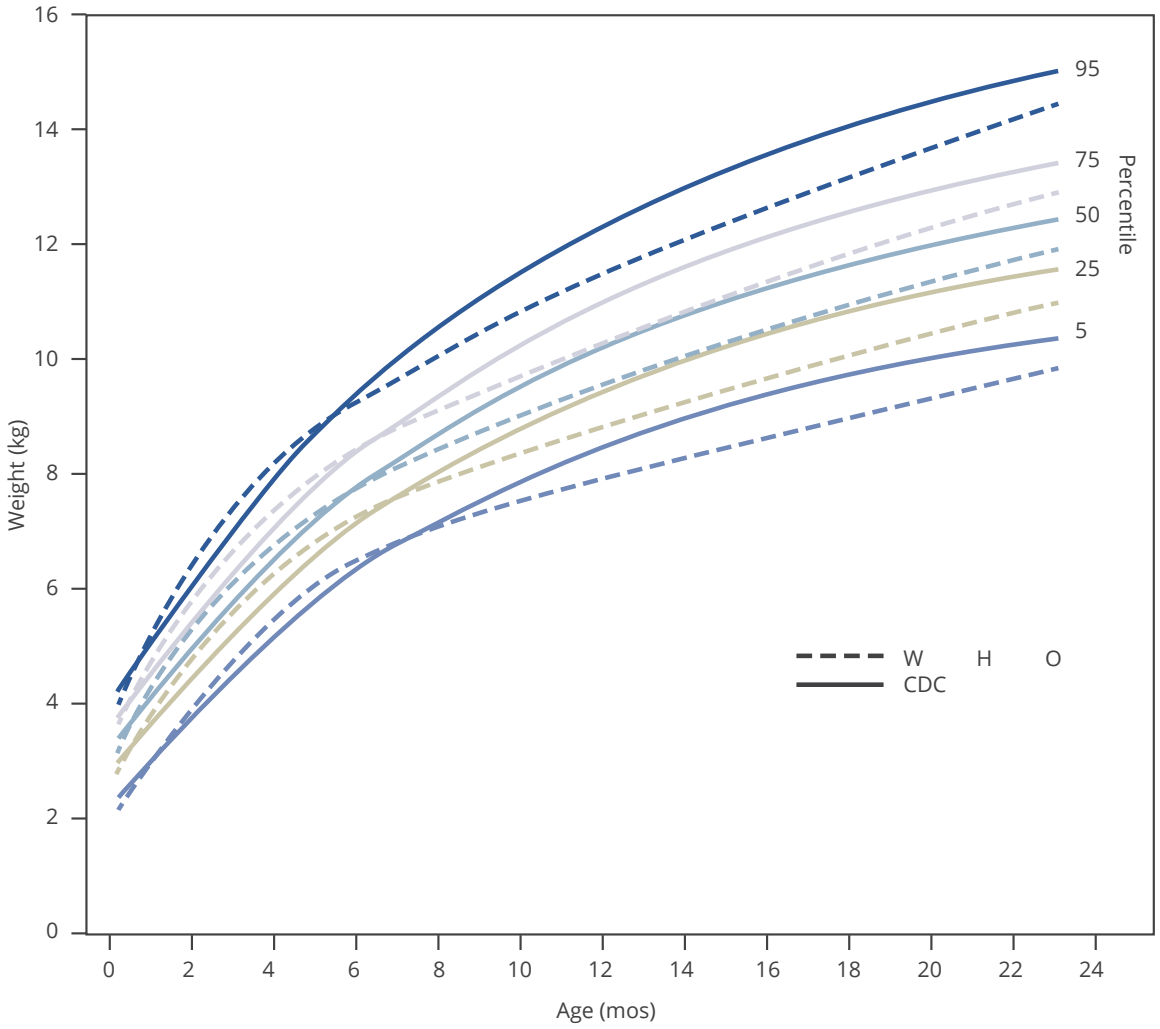

Figure 2- Comparison of World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) growth chart weight-for-age measurements for boys aged <24 months

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(FOOTNOTES)

1 There is ongoing debate regarding conversion factors for carotenoids. Australia and NZ have maintained traditional conversion rates more aligned with sources of carotenoids in our diet, whereas conversion rates are double in the US. Note 1 RAE = 1 µg retinol= 12 µg β-Carotene

cystic fibrosis nutrition

AUSTRALIA - NEW ZEALAND

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