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.