CHAPTER 8 FAT SOLUBLE VITAMINS

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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].

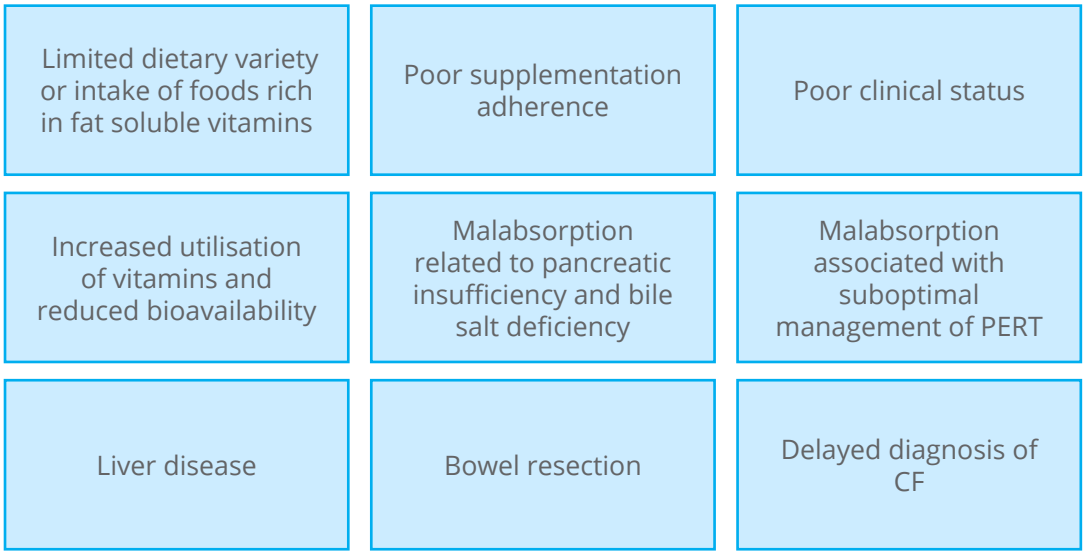

Figure 8a. Potential factors contributing to fat soluble vitamin deficiency in CF

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.