Treating Fat-Soluble Vitamin Deficiencies in Cystic Fibrosis: What are we missing?

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Vitamin Deficiencies

- Deficiencies exist despite routine supplementation

- Clinical Symptoms of Deficiency
  - Vitamin A  Night blindness
  - Vitamin D  Osteoporosis
  - Vitamin E  Neurological abnormalities
  - Vitamin K  Bruising and hemorrhage, osteoporosis
Many additional nutrients may be absorbed from the ileum depending on transit time.

### CF Vitamin Dosing Guidelines 2018

Listed below is the minimum dosing required of each CF vitamin product to meet consensus recommendations for vitamins A, D, E, & K.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>AquADEK</th>
<th>GamADEK</th>
<th>MVW Complete Formulation</th>
<th>ChoiceFull</th>
<th>H2-Pharma</th>
<th>DEKAs-Plus</th>
<th>DEKAs-Essential</th>
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<tbody>
<tr>
<td><strong>Recommended Dose for CF IV</strong> (age levels adjusted accordingly)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;12 months</td>
<td>Liquid</td>
<td>Chew</td>
<td>Liquid</td>
<td>Chew</td>
<td>Liquid</td>
<td>Chew</td>
<td>Liquid</td>
</tr>
<tr>
<td>Vitamin A (IU)</td>
<td>1000</td>
<td>250</td>
<td>500</td>
<td>125</td>
<td>400</td>
<td>100</td>
<td>250</td>
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<tr>
<td>Vitamin D (IU)</td>
<td>800-2000</td>
<td>200</td>
<td>500</td>
<td>125</td>
<td>400</td>
<td>100</td>
<td>250</td>
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<tr>
<td>Vitamin E (IU)</td>
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<td>250</td>
<td>62.5</td>
<td>150</td>
<td>37.5</td>
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<tr>
<td>Vitamin K (mg)</td>
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<td>1.25</td>
<td>3.125</td>
<td>0.78125</td>
<td>2</td>
<td>0.5</td>
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<td><strong>1-2 years</strong></td>
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<td>Vitamin D (IU)</td>
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<td>312.5</td>
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<td>200</td>
<td>50</td>
<td>125</td>
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<td>Vitamin E (IU)</td>
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<td>93.75</td>
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<td>100</td>
<td>250</td>
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<td>Vitamin K (mg)</td>
<td>10-20</td>
<td>2.5</td>
<td>6.25</td>
<td>1.5625</td>
<td>5</td>
<td>1.25</td>
<td>3.125</td>
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<td><strong>3-4 years</strong></td>
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<td>Chew</td>
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<td>200</td>
<td>500</td>
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<tr>
<td>Vitamin D (IU)</td>
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<td>Vitamin E (IU)</td>
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<td>Vitamin K (mg)</td>
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<td>6.25</td>
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<td>Chew</td>
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<td>Chew</td>
<td>Liquid</td>
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<td>Vitamin A (IU)</td>
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<td>750</td>
<td>1875</td>
<td>468.75</td>
<td>1200</td>
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<td>750</td>
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<td>Vitamin D (IU)</td>
<td>2000-4000</td>
<td>500</td>
<td>1250</td>
<td>312.5</td>
<td>1000</td>
<td>250</td>
<td>625</td>
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<tr>
<td>Vitamin E (IU)</td>
<td>1200-3000</td>
<td>300</td>
<td>750</td>
<td>187.5</td>
<td>1200</td>
<td>300</td>
<td>750</td>
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</table>

**Notes:**

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**MVW Multivitamin Wholesale Reference List**

<table>
<thead>
<tr>
<th>Item #</th>
<th>Description</th>
<th>P/N</th>
<th>UPC</th>
<th>Reimbursement Code</th>
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<td>0444401</td>
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</table>

**TABLE 3.** Vitamin D intakes and treatment recommendations for vitamin D deficiency in children and adults with CF

<table>
<thead>
<tr>
<th>Age</th>
<th>Routine dosing with CF-specific vitamins (IU)</th>
<th>Step 1: dose increases (IU)</th>
<th>dose titration maximum (IU)</th>
<th>Step 3</th>
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<tbody>
<tr>
<td>&gt;16 months</td>
<td>400-500</td>
<td>800-1000</td>
<td>Not more than 2,000</td>
<td>Refer</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>800-1,000</td>
<td>1,600-2,000</td>
<td>Not more than 4,000</td>
<td>Refer</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>1,600-2,000</td>
<td>3,200-4,000</td>
<td>Not more than 10,000</td>
<td>Refer</td>
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<tr>
<td>&gt;18 years</td>
<td>3,200-4,000</td>
<td>6,400-8,000</td>
<td>Not more than 10,000</td>
<td>Refer</td>
</tr>
</tbody>
</table>

Revised 11-27-18
Vitamin A

- Retinol
- Absorbed in small intestine
- Stored in liver as retinyl esters
- Metabolism
  - Retinol binding protein (RBP) is a carrier protein
  - Zinc needed to make RBP
  - Prealbumin (TTR) is also a carrier protein
  - RBP: vitamin A: prealbumin occur in a 1:1:1 ratio
Vitamin A

- **Deficiency**
  - Night blindness (rhodopsin), poor bone growth, embryonic development, immune function

- **Toxicity (levels 114-143 mcg/dL)**
  - Causes birth defects, bone pain, liver damage, poor growth
  - High levels may occur after lung transplant (Transplantation 2005, 2011)

- **CF vitamins contain retinol and beta-carotene**
  - Beta carotene is converted to retinol in the gut, regulated by body
  - Only retinol could lead to toxicity
Vitamin A - Serum Levels

- Serum retinol
- Ideally
  - No vitamins the morning of lab draw
  - Fasting
    - Non-fasting sample can be ~20% false increase
    - Inquire whether your lab’s reference ranges were derived from fasting or non-fasting samples
    - Pair with fasting for annual OGTT for >10 yrs CF patients
- Mayo Lab Ranges
  - Reference values were established in patients who were fasting
  - 0-6 years: 11.3-64.7 mcg/dL
  - 7-12 years: 12.8-81.2 mcg/dL
  - 13-17 years: 14.4-97.7 mcg/dL
  - > or =18 years: 32.5-78.0 mcg/dL
Vitamin A - Serum Levels

- Do not check level at beginning of exacerbation/hospitalization
- Levels may be falsely low
  - Depression of retinol as an acute phase response
  - Retinol consumption with infection
- Can measure C-reactive protein (CRP) to evaluate
  - If CRP is high, vitamin A value is falsely low
- Duncan et al 2012
  - If CRP > 10 mg/L then retinol level is affected
  - If CRP > 80 mg/L, there is 50% reduction in serum retinol
- Thurnham et al 2003
  - If CRP is high, retinol levels are reduced by 11-24%
- Hakim et al 2007
  - Vitamin A value 28 mg/dL during exacerbation increases to 36 mg/dL at 1-month follow-up with no intervention
Vitamin A - Treating Deficiency

- Verify adherence
- No published CF guidelines
    - Retinoids - no randomised or quasi-randomised controlled studies
    - Beta carotene - one study, few conclusions
- UNC guidelines
  - Double the dose that CF vitamin is providing
  - < 5 years add 10,000 units daily for 3 months then recheck
  - > 5 years add 20,000 units daily for 3 months then recheck
Vitamin A - Treating Deficiency

- Dosing forms
  - Beta carotene - choose to avoid toxicity
  - Retinol (retinyl palmitate) - use for short gut who cannot convert
  - Swallow or pierce gel cap and squeeze out liquid
  - Drops 5,000 units per drop
  - Tri-vi-sol liquid 1ml
    - vitamin A 750
    - vitamin D 400 units
    - vitamin C 35 mg
Vitamin A - Persistent Deficiency

- Evaluate patients with *persistently* low vitamin A
  - h/o Bowel Resection (meconium ileus)
    - beta carotene is converted to retinol in the small intestine
    - use retinol (retinyl palmitate) instead of beta carotene
  - Zinc deficiency
    - Vital for forming RBP as carrier protein for vitamin A
    - If zinc is low, there is not enough RBP to circulate retinol and serum level will be low
  - Liver disease
    - Unable to store vitamin A in liver as retinyl esters

- Labs to check
  - Serum zinc
  - C-reactive protein (CRP)
  - Retinol Binding Protein (RBP)
  - Pre-albumin (transthyretin)
Vitamin A: RBP Molar Ratio

- Convert Vitamin A and RBP to the same units $\text{µmol/L (micro-mol/L)}$
  - Retinol ($\text{µg/dL} \times 0.0349 = \text{µmol/L}$)
  - RBP ($\text{mg/dL} \times 0.476 = \text{µmol/L}$)

- Calculate ratio by dividing retinol by RBP
  - $<0.8$ is suggestive of deficiency where you could add more
  - $0.8-1.0$ is Normal
  - $>1.0$ is suggestive of toxicity

- Use the molar ratio of retinol:RBP to guide your dosing
  - If $<0.8$ then you have free RBP available to bind additional retinol; you can give more
  - If $>1$, then the retinol is too high in the blood
    - the RPB carrier is saturated
    - may collect in liver and potentially cause liver damage
  - If $0.8-1.0$, then there are good amounts of both; normal state
  - If RBP is low
    - Do not give $>20,000\text{IU}$ vitamin A
    - Consider zinc supplementation to increase RBP synthesis (1-2 mg/kg/day or DRI)
Vitamin A - Drug Interaction

- **Isotretinoin (Accutane®)**
  - Teenage acne, a retinoid
  - For CF, more likely to cause Vitamin A deficiency
  - Counterintuitive (toxicity is not a concern)
  - Presumed that medicine competes with vitamin A
  - Recommend continue usual CF vitamin supplement and measure serum level during treatment

  - 1 of 9 CF patients had night blindness and low serum level

  - 1 of 11 CF case reports had night blindness with Accutane and resolved with increased vitamin A supplementation
Vitamin A - Case Study

KV is 18 yo female, well nourished

- Low vitamin A level for > 1 year
  - AquADEK 2 gel caps daily, compliant
  - Vitamin A 20,000 units daily, added after first low level
- Vitamin A, serum retinol Reference range
  - for >18 yo 32.5 - 78.0 mcg/dL
  - for 14-17 yo 14.4 - 97.7 mcg/dL
- Lab values
  - (7/31/12) 27.6 mcg/dL normal
  - (6/18/13) 17.4 mcg/dL low
  - (7/03/14) 17.3 mcg/dl low
  - RBP 1.60 mg/dL normal, range 1.5 - 6.7
- Calculations
  - Retinol = 17.3 \times 0.0349 = 0.60377
  - RBP = 1.60 \times 0.476 = 0.7616
  - Molar ratio = 0.792
- Because there is more RBP than retinol, you can increase dose of vitamin A supplement.
  - There is plenty of RBP to carry additional retinol
  - RBP is in the normal range
Vitamin A - Case Study

- JK transferred to our CF center, s/p liver transplant
- Low serum vitamin A
  - Transplant center wanted caution with vitamin A to maintain healthy liver
  - High dose supplementation did not improve serum level
    - 3/2017 38,000 units vit A, 20% retinol (2 AquADEK chews + 20,000 beta-carotene)
    - 4/2017 56,000 units vit A, 20% retinol (4 AquADEK chews + 20,000 beta-carotene)
    - 10/2017 32,000 units vit A, 20% retinol (1 MVW gel + 16,000 beta-carotene)
    - 11/2017 34,508 units vit A, 100% retinol (H2Pharma 4ml + 16,000 retinyl palm)
      - MD mentioned history of meconium ileus and intestinal resection
      - Retinol Binding Protein (RBP) <1.3 and vitamin A <5.0
        - unable to calculate ratio; add zinc 1 mg/kg/day
  - 01/2018 Normal level while on 24,000 units vit A, 100% retinol + zinc
    - Normal range, 14.4-97.7 mcg/dL
Vitamin D
Vitamin D

- **Forms**
  - D3 Cholecalciferol
  - D2 Ergocalciferol

- **Sources**
  - diet
  - sunlight

- **Functions**
  - promotes calcium absorption in the gut
  - normal mineralization of bone
  - modulation of cell growth
  - neuromuscular and immune function
  - reduction of inflammation

- **Metabolism**
  - must undergo two hydroxylations in the body for activation
  - liver converts to 25-hydroxyvitamin D, calcidiol
  - kidney forms active 1,25-dihydroxyvitamin D, calcitriol
Vitamin D - Assessment

- Measure serum total 25-OH vitamin D level
  - best indicator of vitamin D status
    - reflects vitamin D produced cutaneously plus from food and supplements
    - has a fairly long circulating half-life of 15 days
  - Reports the sum of D2 and D3
    - Minimum >30 ng/mL (75 nmol/L)
    - Optimal 30-60ng/mL (75-150 nmol/L)
    - Okay up to 100ng/mL (250 nmol/L)
  - Serum PTH rises with Vitamin D < 30 ng/mL
  - Variability based on season and latitude
- Do not measure serum 1,25 vitamin D
  - has a short half-life of 15 hours
  - serum concentrations are regulated by PTH, calcium, & phosphate
  - levels do not decrease until vitamin D deficiency is severe

- Account for current CF vitamin dose when adding more
- Extra supplement required becomes maintenance dose

**TABLE 3.** Vitamin D intakes and treatment recommendations of vitamin D deficiency in children and adults with CF

<table>
<thead>
<tr>
<th>Age</th>
<th>Routine dosing with CF-specific vitamins (IU)</th>
<th>Step 1: dose increases (IU)</th>
<th>Step 2: dose titration maximum (IU)</th>
<th>Step 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 12 months</td>
<td>400–500</td>
<td>800–1,000</td>
<td>Not more than 2,000</td>
<td>Refer</td>
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<tr>
<td>&gt;12 months to 10 yr</td>
<td>800–1,000</td>
<td>1,600–3,000</td>
<td>Not more than 4,000</td>
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<tr>
<td>&gt;10 yr to 18 yr</td>
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<td>1,600–6,000</td>
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<tr>
<td>&gt;18 yr</td>
<td>800–2,000</td>
<td>1,600–6,000</td>
<td>Not more than 10,000</td>
<td>Refer</td>
</tr>
</tbody>
</table>
Vitamin D - Treatment

- **D3 Cholecalciferol**
  - Many OTC products in US
  - In “CF vitamins”
  - Tablets and soft gels 400, 1000, 2000, 5,000 units
  - Replesta ® 50,000unit orange flavored wafer
  - D-vi-sol liquid for infants (Enfamil), 400units/ml
  - D-drops from Carlson varying concentrations

- **D2 Ergocalciferol**
  - OTC
    - Tablets or softgels
    - Liquid suspension Calciferol ® Drops, 8000units/mL
  - Prescription
    - 50,000unit capsule, Drisdol ®
Vitamin D - case study

- KDG now 18 yo male with CF, BMI >50thile, on ivacaftor
- Vitamin D less than 30, persistent
- Darker skin, spends most of time indoors
- Vitamin D supplement
  - 7,000 units D3/chole
  - 10,000 units D3/chole
  - 10,000 units D3/chole + 50,000 twice weekly D2/ergo
  - Moderate adherence
- Now considering modified Stoss therapy (high dose given in clinic)

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<td>21</td>
<td>10</td>
<td>na</td>
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<td>Na</td>
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</table>
Vitamin E
Vitamin E

- Family of tocopherols and tocotrienols
  - exists in eight chemical forms
    - alpha-, beta-, gamma-, and delta-tocopherol
    - alpha-, beta-, gamma-, and delta-tocotrienol
  - alpha tocopherol is the form that can meet human needs
  - liver preferentially re-secretes only alpha-tocopherol

- Functions
  - Antioxidant
  - Immune System
  - Normal neurological function, cognitive development
Vitamin E - Assessment

- Measure “serum Vitamin E”
  - usually alpha tocopherol
  - At UNC, lab is a send out to Mayo who measures alpha-tocopherol

- Serum levels are relative to total lipids
  - confounded by low vs. high cholesterol levels in CF
- Three ratios to adjust for lipids
  - alpha tocopherol : total lipid (cholesterol+triglyceride+phospholipid)
  - alpha tocopherol : (cholesterol + triglyceride)
    - Use for CF adults (normal range 1.42-5.71 mg/g)
  - alpha tocopherol : cholesterol
    - Use for CF children (normal range 3.8-6)
    - Huang SH et al. J Pediatr 2006 Apr
Vitamin E - Evaluation

- Elevated values common post lung transplant
  - Transplantation 2005, 2011
- Falsely elevated levels caused by
  - Non fasting or less than 12-14 hour fast
  - Patient takes vitamins the morning of lab draw
- Falsely low levels caused by
  - Exacerbation (same as Vitamin A)
  - Degradation may occur if sample not protected from light
    - Collected in an amber vial (dark colored) or wrapped
    - Usually lab will not accept if this is case
Vitamin E - Deficiency

- Treat deficiencies
  - No published CF guidelines
  - UNC guidelines
    - < 5 years add 400 units daily for 1-3 months then recheck
    - > 5 years add 800 units daily for 1-3 months then recheck
- Dosing forms
  - Most OTC is alpha tocopherol
  - OTC capsules (swallow or pierce)
  - OTC Aqua-E (Yasoo) 100 units/ml
    - water-soluble form
    - tocopheryl polyethylene glycol-1000 succinate (TPGS)
Vitamin E - Adjusted for Lipids

- Adjusts level for patient’s lipid level
  - High lipids can result in falsely high vitamin E levels
  - Low lipids can result in falsely low vitamin E levels
- Fasting lab draw: Vitamin E, cholesterol, triglycerides

Calculate Ratio (mg/g) = \( \frac{\text{vitamin E (mg/L)}}{\text{Total cholesterol + triglycerides (g/L)}} \)

Interpretation
- Normal range 1.42-5.71 mg/g (adults)
- If < 0.8 mg tocopherol/gm lipid = definite deficiency
- If ratio is normal, then do not change vitamin E dose
- If ratio is low, then increase vitamin E dose (true deficiency)
- If ratio is high, then decrease vitamin E dose (true toxicity)
**Vitamin E - Case Studies**

**Example 1: RT**

<table>
<thead>
<tr>
<th>Vitamin E</th>
<th>34.3 mg/L</th>
<th>High, persistent</th>
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<tbody>
<tr>
<td>Cholesterol</td>
<td>240 mg/dL</td>
<td>High</td>
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<tr>
<td>Triglycerides</td>
<td>675 mg/dL</td>
<td>High</td>
</tr>
</tbody>
</table>

**Calculation**

\[
\text{Calculation} = \frac{34.3 \text{ mg/L}}{9.15 \text{ g/L}}
\]

\[
= 3.7 \text{ mg/g normal (range 1.42-5.71 mg/g)}
\]

Her serum vitamin E level is elevated due to high TG and cholesterol. Her current vitamin E dose is adequate and should not be changed.

**Example 2: JB**

<table>
<thead>
<tr>
<th>Vitamin E</th>
<th>11.4 mg/L</th>
<th>Normal</th>
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</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>174 MG/DL</td>
<td>Normal</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>175 MG/DL</td>
<td>High</td>
</tr>
</tbody>
</table>

**Calculation**

\[
\text{Calculation} = \frac{11.4 \text{ mg/L}}{3.49 \text{ g/L}}
\]

\[
= 3.2 \text{ mg/g normal (range 1.42-5.71 mg/g)}
\]

She has new onset of neurological symptoms and Neurologist raises concern for Vitamin E deficiency.
Vitamin K
Vitamin K

Two naturally occurring forms of vitamin K

- Vitamin K\textsubscript{1}
  - phylloquinone
  - synthesized by plants & the predominant form in our diet
  - phytonadione is the synthetic form of K\textsubscript{1} (Mephyton)

- Vitamin K\textsubscript{2}
  - menaquinones, a range of vitamin K forms
  - comes from animal sources
  - synthesis by intestinal bacteria

Functions

- Blood clotting
- Bone mineralization

Deficiency: bleeding, bruising, bone disease
Vitamin K

- Deficiency still occurs despite taking CF vitamins

- n=97 CF & PI
- Measured diet, vitamin K supplement, PIVKA-II, %ucOC,
- Patients on “CF vitamins” still showed signs of deficiency
- Only those taking >1000 mcg/day achieved a levels of healthy subjects
- CF vitamin content varies 300 - 1000 mcg
Vitamin K - Lab Assessment

- Measures
  - Indirect: Prothrombin Time
    - a late marker of severe deficiency
    - “cheap” and practical as a first-line assessment
    - high value indicates deficiency
  - Direct: DCP (formerly PIVKA-II)
    - Des carboxy prothrombin (DCP)
    - PIVKA-II: Proteins induced in vitamin K absence
    - high value indicates deficiency
    - early and sensitive marker, more expensive send-out
  - Less useful
    - Serum vitamin K₁: recent intake affects levels in serum
    - Percent Undercarboxylated Osteocalcin (%ucOC): low BMD
Vitamin K - Treatment

- Treat deficiencies
  - No standard guidelines
  - At UNC
    - Give 5mg daily x 2 weeks and recheck PT (inpatient)
    - If no improvement can increase to 10mg daily
    - If no improvement check DCP (PIVKA-II)
  - We often give prophylactic dose with IV antibiotics r/t loss of bacterial production in gut
- Prescription products
  - Tablet 5mg (5,000mcg) and 100 mcg (mephyton, phytonadione)
  - Injectable 2mg/mL and 10mg/mL (aqua-mephyton)
- OTC products
  - Tablets 45 to 500 mcg (common 100 mcg and 200 mcg)
Vitamin K - Case Study

JB

- 18 yo male with CF, PS
- Persistently elevated PT x > 4 values
- On CF vitamin plus 10mg daily phytonadione

Why would a pancreatic sufficient patient require so much vitamin K?

- Check of DCP normal <0.2 (normal, range <6.3)
Vitamin K - Case Study

JG

- 16 yo male with persistently elevated PT
  - Adherent to 10mg daily phytonadione + 2 AquaADEK gels
  - Checked DCP = <0.2 normal (normal range <7.5)

- Hematology workup
  - Differential diagnosis is severe Vitamin K malabsorption or congenital Factor 7 deficiency
  - Given IV vitamin K x 3 doses to r/o malabsorption, but PT same

- PO vitamin K dose decreased to 5mg daily
  - Then decreased to 5 mg three times a week

- For procedures, he is given Novo7 (Coagulation Factor VIIa; recombinant) pre and intra-operatively.
References - Vitamins


References - Vitamins


Fat-Soluble Vitamins

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