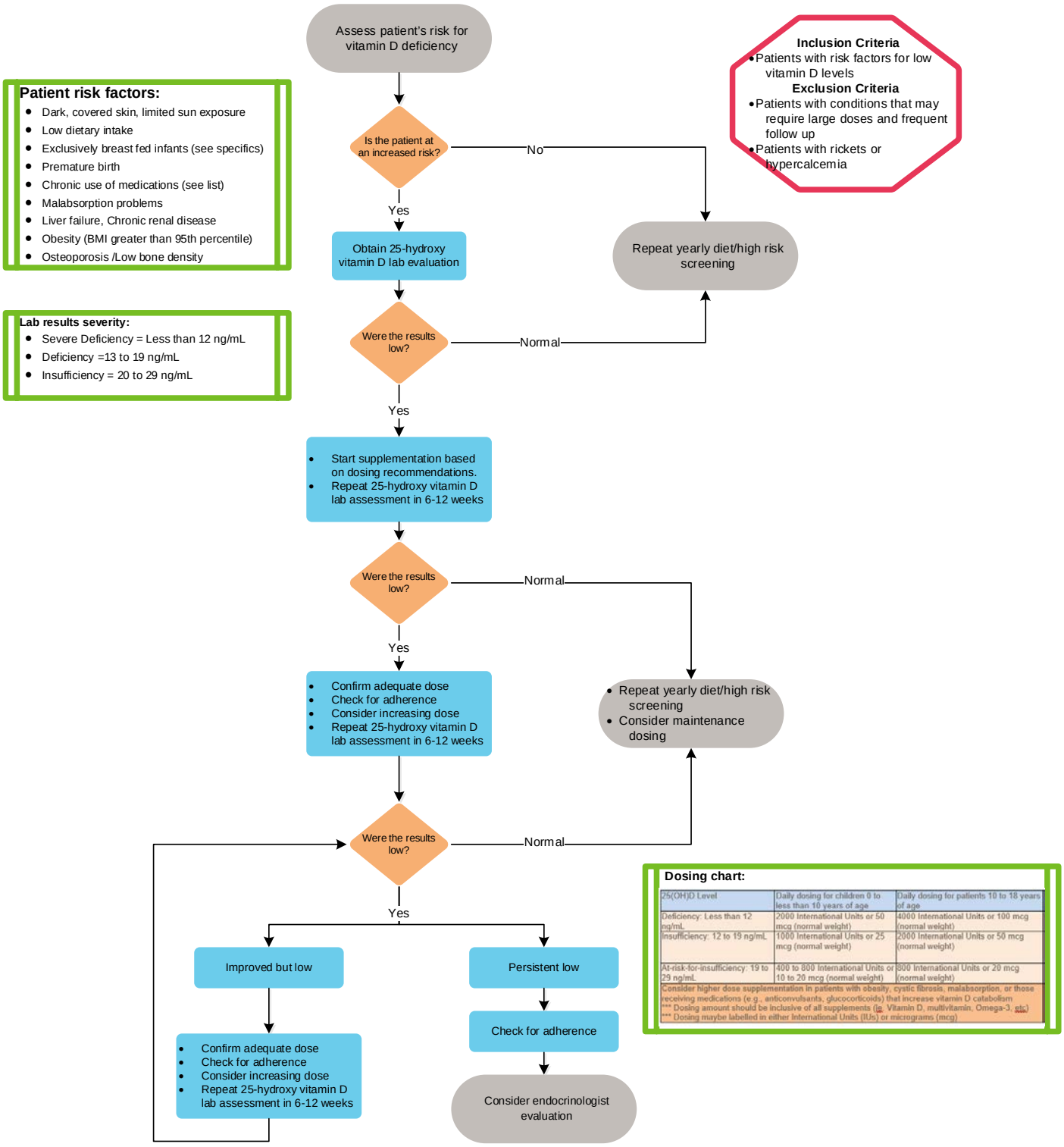
VITAMIN D DEFICIENCY

ALGORITHM



PATHWAY SUMMARY

Assessment

Consider vitamin D screening in children with the following risk factors:

- Dark or covered skin
- Limited sun exposure
- Low dietary intake
- Any breast-fed or formula-fed infant unable to consume at least 1L/day of fortified breastmilk or formula, who is not already supplemented with the recommended Vitamin D dose (400 IU/10 mcg)
- Chronic use of medications that impact vitamin D metabolism or absorption, or greatly increase risk of osteoporosis: including anticonvulsants, glucocorticoids, antifungals and medications used for the treatment of HIV
- Malabsorption problems
- Liver failure
- Obesity (BMI $\geq 95^{th}$ percentile)
- Premature birth
- Chronic renal disease or history of renal transplant
- Osteoporosis
- Low bone density

Laboratory Study

- Request for 1,25-dihydroxyvitamin D will be intercepted by the team and the provider form letter will be sent to the ordering provider

Therapeutics

- The Children's Hospital Colorado Vitamin D Committee recommends that all individuals, who are supplemented, take once-daily vitamin D_3 or its weekly equivalent to maintain serum 25(OH)D levels of at least 30 ng/mL.

Recommendations for follow up:

- Vitamin D levels should be rechecked after 6 to12 weeks of treatment.
- Vitamin D can be evaluated sooner if medically indicated.
- Consider annual surveillance in individuals that remain at-risk for vitamin D deficiency or when optimization of vitamin D status is a treatment goal for bone health.
- Consider Endocrinology referral if deficiency is resistant to treatment, or in patients with osteoporosis and low bone density.

Prevention

Information regarding appropriate sun exposure, the use of vitamin D supplements, and eating a diet rich in calcium and vitamin D should be made available to each patient.

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TARGET POPULATION

Inclusion Criteria

- Patients with risk factors for low vitamin D levels

Exclusion Criteria

- Pediatric patients with chronic medical conditions which may require large doses and more frequent follow up.
- Patients with severe deficiency leading to rickets or other conditions associated with hypercalcemia.

BACKGROUND | DEFINITIONS

Vitamin D is a fat-soluble vitamin that the body makes from cholesterol through the action of the sun's UVB rays on the skin. Factors such as skin color, age, amount and time of sun exposure, and geographic location affect how much vitamin D the body makes. The primary function of vitamin D is to maintain normal blood concentrations of calcium and phosphorus, to support bone health as normal bone mineralization depends on adequate calcium and phosphate[1] Low vitamin D levels may result in decreased calcium and phosphate concentrations, and secondary hyperparathyroidism causing inadequate mineralization and loss of skeletal mass. When growth plates are closed, this can lead to osteomalacia; if the growth plates have not closed, rickets may develop. It has also been suggested that vitamin D may have additional benefits on cardiovascular, pancreatic, muscle and brain health.

RECOMMENDATION FOR SCREENING

Note: Screening for vitamin D levels should be reserved for patients with risk factors for deficiency or when optimization of vitamin D is a treatment goal for bone health. Universal screening of all patients is not recommended[2,3].

Consider assessing vitamin D status in children with the following risk factors:

- Dark skin[1]
- Limited sun exposure, including frequent sunscreen use and cultural convention associated with covering body[3]
- Low dietary intake, including vegan/macrobiotic diets, milk avoiders or patients with allergy/intolerance[3]

- Chronic use of medications that impair vitamin D metabolism or absorption (e.g. anticonvulsants, steroids [including inhaled], antifungals and medications used for the treatment of HIV)[2]
- Malabsorption problems (including celiac disease, cystic fibrosis, etc.)[2]
- Obesity[1] (95th percentile)
- Premature birth[3]
- Infants of breastfeeding mothers with dark skin or covered (minimal skin exposure) without vitamin D supplementation or low intake of foods containing vitamin D. Any breast-fed or formula-fed infant unable to consume at least 1L/day of fortified breastmilk or formula is at increased risk of vit D deficiency[3].
- Malabsorption problems
- Chronic renal disease or history of renal transplant
- Liver failure
- Chronic renal disease or history of renal transplant
- Osteoporosis
- Low bone density

LABORATORY STUDIES

Vitamin D levels are measured by total serum 25-hydroxyvitamin D [also referred to as 25(OH)D][2]. Testing 25-hydroxyvitamin D is most useful in nutrition assessment, primarily due to its longer half-life and minimal effect of parathyroid hormone on circulating levels.

Since the development of 1,25-***di***hydroxyvitamin D testing, proper utilization based on clinical need has been problematic. The circulating half-life of 1,25-dihydroxyvitamin D is relatively short, which limits utility for overall vitamin D assessment. 1,25-dihydroxyvitamin D testing can be useful in the diagnosis of renal dysfunction in conjunction with parathyroid hormone, as well as in specific disorders of mineral metabolism.

Laboratory Approval Process

Test requests for 1,25-dihydroxyvitamin D will be flagged for review by the lab and sent to the ordering provider for review.

- Laboratory team responsibility:
  - Request for 1,25-dihydroxyvitamin D will be intercepted by the team and the provider form letter will be sent to the ordering provider.
  - After the ordering provider responds with their decision, the lab team will either:
    - Send the specimen for processing

      OR

    - Cancel the request and redirect, to 25(OH)D testing
- The lab team will document the case and decision in their database
- Provider responsibility:
  - In the event the ordering provider does not respond within two days, the request will be sent to the on-call provider for the group.
  - The on-call provider can decide to approve the testing or redirect testing if clinically indicated

Evaluation of Laboratory Results

- **Vitamin D status as measured by 25(OH)D:** (interpretation should take into account time of year, skin color, and presence of obesity or medical condition)
- Severe Deficiency = Less than 12 ng/mL
  - At-risk for rickets, defective bone mineralization, and fractures
- Deficiency =13 to 19 ng/mL
- Insufficiency = 20 to 29 ng/mL
  - At-risk for secondary hyperparathyroidism and decreased bone mineral density
- Sufficiency = 30 to 100 ng/mL
- Toxicity = Greater than100 ng/mL
  - Hypercalcemia
    - Gastrointestinal distress, bone pain
  - Hypercalciuria
  - Kidney stones
  - Hyperphosphatemia

THERAPEUTICS

Recommendations for supplementation:

These recommendations do not differentiate between the use of cholecalciferol (D_3) or ergocalciferol (D_2), as there is insufficient data to show any significant difference in absorption, particularly at therapeutic levels[5]. For patients who require large weekly doses (i.e., 50,000 International Units$_2$) is preferred: however, it should be noted that patient insurance may require prescription and prior authorization (PAR). The American Academy of Pediatrics recommends daily dosing; however, the dosing schedule (daily versus weekly) should be individualized to minimize financial issues and treatment burden, particularly in patients with chronic illness[6]. Other considerations include the potential for vitamin D toxicity if a weekly high-dose regimen is inadvertently continued or possible loss of efficacy if the weekly dose is missed. The Children's Hospital Colorado Vitamin D Committee recommends that all individuals, who are supplemented, take once-daily vitamin D_3 or its weekly equivalent to maintain serum 25(OH)D levels of at least 30 ng/mL.

Table 1. Dosing Recommendations for Treatment

25(OH)D Level	Daily dosing for children 0 to less than 10 years of age	Daily dosing for patients 10 to 18 years of age
Deficiency: Less than 12 ng/mL	2000 International Units or 50 mcg (normal weight)	4000 International Units or 100 mcg (normal weight)
	4000 International Units or 100 mcg (obese, BMI greater than 95%)	8000 International Units or 200 mcg (obese, BMI greater than 95%)
Insufficiency: 12 to 19 ng/mL	1000 International Units or 25 mcg (normal weight)	2000 International Units or 50 mcg (normal weight)
	2000 International Units or 50 mcg (obese BMI greater than	4000 International Units or 100 mcg (obese, BMI greater than 95%)

	95%)	
At-risk-for-insufficiency: 19 to 29 ng/mL	400 to 800 International Units or 10 to 20 mcg (normal weight)	800 International Units or 20 mcg (normal weight)
	1000 International Units or 25 mcg (obese, BMI greater than 95%)	1000 International Units or 25 mcg (obese, BMI greater than 95%)
Consider higher dose supplementation in patients with obesity, cystic fibrosis, malabsorption, or those receiving medications (e.g., anticonvulsants, glucocorticoids) that increase vitamin D catabolism *** Dosing amount should be inclusive of all supplements (ie. Vitamin D, multivitamin, Omega-3, etc) *** Dosing maybe labelled in either International Units (IUs) or micrograms (mcg)		

Recommendations for follow up:

- Vitamin D levels should be rechecked after 6 to12 weeks when supplementation is initiated, or with any dose change.
- Vitamin D can be evaluated sooner if medically indicated. A dose response to therapy should be evident on laboratory evaluation within 4 to 6 weeks of supplementation.
- Patients with chronic illness (CF, renal disease, etc.) should have their vitamin D levels checked annually as part of routine health maintenance, and regardless of supplementation status.
- Consider Endocrinology referral if deficiency is resistant to treatment or patient has documented rickets that is not associated with vitamin D deficiency (hypophosphatemic rickets). Children's Hospital Colorado Endocrinology department is available for phone consultation at any time with questions or concerns (720-777-6128).

PREVENTION

Information regarding appropriate sun exposure, the use of vitamin D supplements, and eating a diet rich in calcium and vitamin D should be made available to each patient.

Prevention and maintenance measures to avoid deficiency (or recurrent deficiency) through vitamin D supplementation are suggested as follows:

Breast feeding infants or infants unable to consume 1 L of fortifed breast milk or formula, up to 12 months old: 400 International Units/day

0-12 mo: 400-1,000 International Units/day or 10-25 mcg/day

1-18 yo: 800-1,000 International Units/day or 20-25 mcg/day

Pregnancy and Lactation: 800-1,000 International Units/day or 20-25 mcg/day

19-50 yo: 1,500-2,000 International Units/day 37.5-50 mcg/day

Patients with at-risk medical conditions (e.g. premature infants, obesity, cystic fibrosis, malabsorption, etc.) or are taking medications that enhance vitamin D catabolism, may require higher maintenance doses and more frequent follow up.

FREQUENTLY ASKED QUESTIONS

What are the forms of vitamin D?

- Cholecalciferol (vitamin D_3)
  - A naturally occurring form of vitamin D made by the skin upon sun exposure (UVB rays)
  - Found in some foods and most supplements, including cod liver oil
- Calcidiol (25-hydroxyvitamin D) - this is the lab measurement for Vitamin D status
  - A pre-hormone made directly from cholecalciferol primarily in the liver
  - Low bio-activity, but a major circulating form in the blood stream
- Calcitriol (1,25 dihydroxyvitamin D_3)
  - The activated form of vitamin D made from calcidiol primarily in the kidneys Ergocalciferol (vitamin D_2)
  - Not naturally occurring in the body, generally plant derived and made in the laboratory. Used in some supplements

Is there a difference between the forms of Vitamin D in supplements?

- There are two main forms of vitamin D in supplements: cholecalciferol and ergocalciferol There is insufficient evidence to suggest one form of vitamin D is more effective than the other in increasing and maintaining sufficient levels of vitamin D

What is the controversy regarding vitamin D "sufficiency"?

- There is a lack of consensus on what is the optimal vitamin D level and vitamin D requirement for children and adolescents. There often isn't a specific level above which one is protected, nor is there a level at which disease is inevitable. Treating to a 25(OH)D level greater than 30 ng/mL may not produce additional skeletal benefits above treating to a level of greater than 20 ng/mL; however, the health risks of doing so appear to be minimal though therapy may be expensive for patients

Are there medications that make a patient more "at risk"?

- Any medication that increases vitamin D catabolism or results in decreased vitamin D absorption can increase risk. Several of these are
- Corticosteroids (including inhaled formulations)
  - Reduce calcium absorption and increase destruction of vitamin D
- Bile acid sequestrants (e.g., cholestyramine)
  - May impair absorption of vitamin D
  - Vitamin D should be taken at least 1 hour before or 4-6 hours after bile acid sequestrants
- Orlistat
  - May impair absorption of vitamin D
  - Vitamin D should be taken at a different time than Orlistat
- Anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine)
  - Increase the destruction of vitamin D to inactive compounds
- Antimicrobials (e.g. rifampin, ketoconazole)
  - Increase the destruction of vitamin D to inactive components (rifampin)
  - Prevent conversion of 25(OH)D to the active 1,25-dihidroxyvitamin D_3 (ketoconazole)
- Antiretrovirals (e.g. efavirenz, ritonavir)
  - Increase the destruction of vitamin D to inactive components (efavirenz)
  - Prevent conversion of 25(OH)D to the active 1,25-dihidroxyvitamin D_3 (ritonavir)Is there a specific time my patients should take their supplement?

- We advise taking vitamin D supplements daily, preferably with the largest meal of the day to improve absorption.

Should I advise my patients to get more sun?

- Unprotected sun exposure (UVB rays):
    - Sensible sun exposure can provide adequate amounts of vitamin D. However, multiple factors reduce cutaneous synthesis of vitamin D including, skin pigment, sunscreen use, season, latitude, and time of day. Individuals at increased risk for skin damage or cancer may benefit from vitamin D supplementation[9]

Should I screen for metabolic causes or underlying malabsorption if my patient is deficient?

- Most patients do not have any other disease processes causing their vitamin D deficiency, and thus lead to unnecessary evaluation. Consider additional screening, **only** for patients with signs or symptoms suggesting underlying disease processes (e.g. diarrhea, weight loss, poor growth, multiple fractures).

If my patient has vitamin D deficiency, should I screen for osteoporosis?

- Osteoporosis is a clinical diagnosis. Additional testing is **only** indicated if clinical history (multiple fractures, vertebral compression fractures, etc.) is suggestive of skeletal fragility.

When should I repeat laboratory evaluation after starting supplementation?

- Labs should be repeated in 6 to 12 weeks, sooner if medically indicated.

Does insurance typically cover supplementation?

- Insurance usually does not cover vitamin D supplementation. Very high doses (e.g., 50,000 International Units) may be available through prior authorization (PAR), but are not typically recommend except in cases of severe deficiency.

PARENT AND PROVIDER EDUCATION MATERIALS

Handouts:

- Vitamin D supplements
- Dosing chart
- Table of dietary vitamin D

APPENDIX A. SAMPLE LABORATORY TEST LETTER

Dear Provider,

Our lab received a request for 1,25-dihydroxyvitamin D for your patient, {Name, DOB}. This request requires review before it will be sent for processing. Recent studies found that more than 50% of orders were placed in error, where 25-hydroxyvitamin D was the intended test to assess nutritional status.

25-hydroxyvitamin D is most useful in nutrition assessment, primarily due to its longer half-life. It is elevated with vitamin D intoxication, and decreased with malabsorption, nutritional deficiency, and in liver disease. This test is performed daily in Children's Hospital Colorado Laboratory.

The circulating half-life of 1,25-dihydroxyvitamin D is relatively short, which limits utility for overall vitamin D assessment. Testing can be useful in the diagnosis of renal dysfunction in conjunction with parathyroid hormone. 1,25-dihydroxy is elevated in sarcoidosis and primary hyperparathyroidism, and decreased in renal failure and hypoparathyroidism. 1,25-dihydroxyvitamin D may be a valuable test in the evaluation of mineral metabolism disorders.

There are two options for how to proceed with this test:

- We can cancel the order for 1,25-dihydroxyvitamin D and you can write an add-on communication for 25 hydroxyvitamin D- we do not need a new order or specimen.
- Proceed with the test as you have ordered it.

Please let us know if we can be helpful and how you want to proceed. We apologize for any inconvenience if this was the test you intended.

Sincerely,

The Laboratory Team and Vitamin D Committee at Children's Hospital Colorado

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CLINICAL IMPROVEMENT TEAM MEMBERS

Kimberly Gracey, PA-C | Clinical Nutrition
Helen Seagle, MS, RD, CSP | Clinical Nutrition
Nancy Krebs, MD (Section Head) | Clinical Nutrition
Liliane Diab, MD (Associate Medical Director) | Clinical Nutrition
Susan Marshall, MS, RD, CSP | Clinical Nutrition (NICU)
Nina MA, MD | Endocrinology
Sarah Bartz, MD | Endocrinology
Magda Nowinski, PharmD | Pharmacy
Liz Ficco | Clinical Effectiveness

MANUAL/DEPARTMENT	Clinical Pathways/Quality
ORIGINATION DATE	November 3, 2014
LAST DATE OF REVIEW OR REVISION	August 25, 2020
COLORADO SPRINGS REVIEW BY	 Michael DiStefano, MD Chief Medical Officer, Colorado Springs
APPROVED BY	 Lalit Bajaj, MD, MPH Medical Director, Clinical Effectiveness

REVIEW/REVISION SCHEDULE

Scheduled for full review on August 25, 2024

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