VITAMIN D DEFICIENCY

CHI Formulary Treatment Algorithm

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Supporting treatment algorithm for the clinical management of Vitamin D Deficiency

The figure below outlines a comprehensive treatment algorithm on the therapy for Vitamin D Deficiency, aimed at addressing the different lines of treatment after thorough review of medical and economic evidence by CHI committees.

For further evidence, please refer to CHI Vitamin D Deficiency full report. You can stay updated on the upcoming changes to our formulary by visiting our website at https://chi.gov.sa/AboutCCHI/CCHIprograms/Pages/IDF.aspx

Our treatment algorithm offers a robust framework for enhancing patient care and optimizing treatment outcomes across a range of treatment options, holding great promise for improving healthcare delivery.

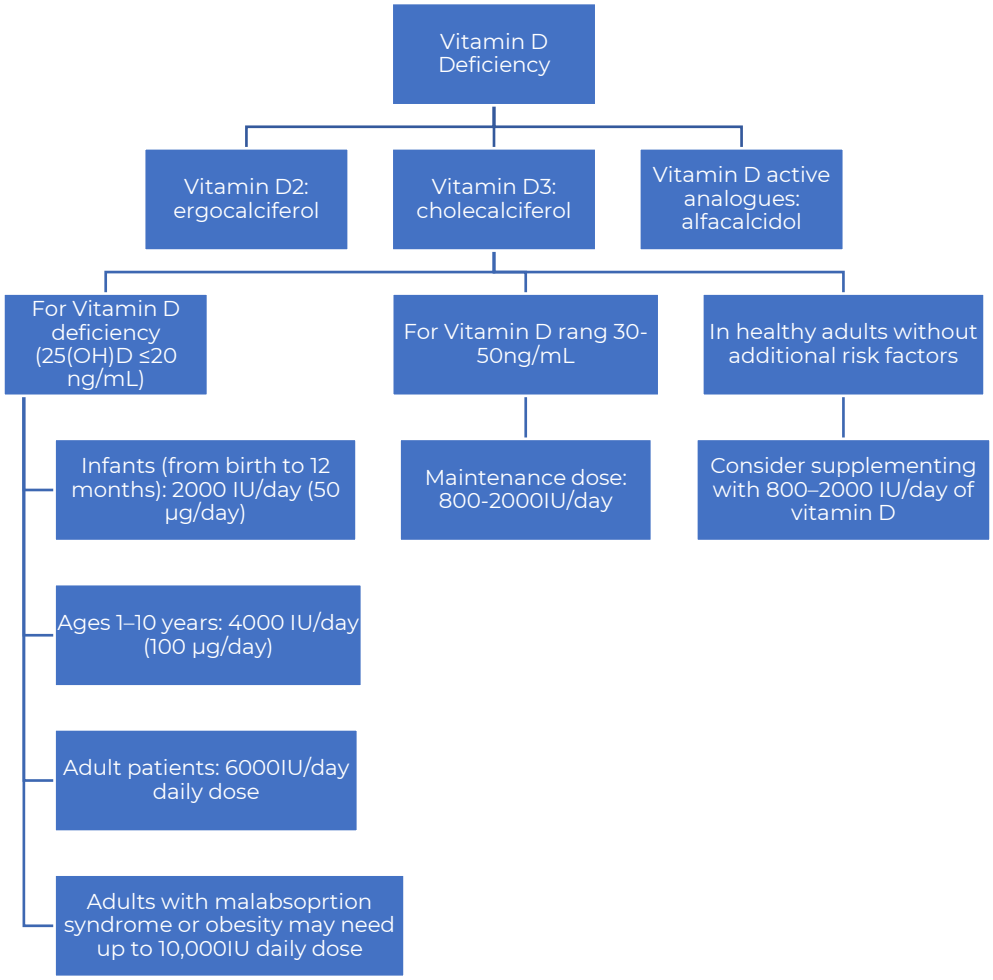

Figure 1. *Treatment Algorithm for the Management of Vitamin D Deficiency*

Based on the Clinical Practice in the Prevention, Diagnosis and Treatment of Vitamin D Deficiency: A Central and Eastern European Expert Consensus Statement (2022)

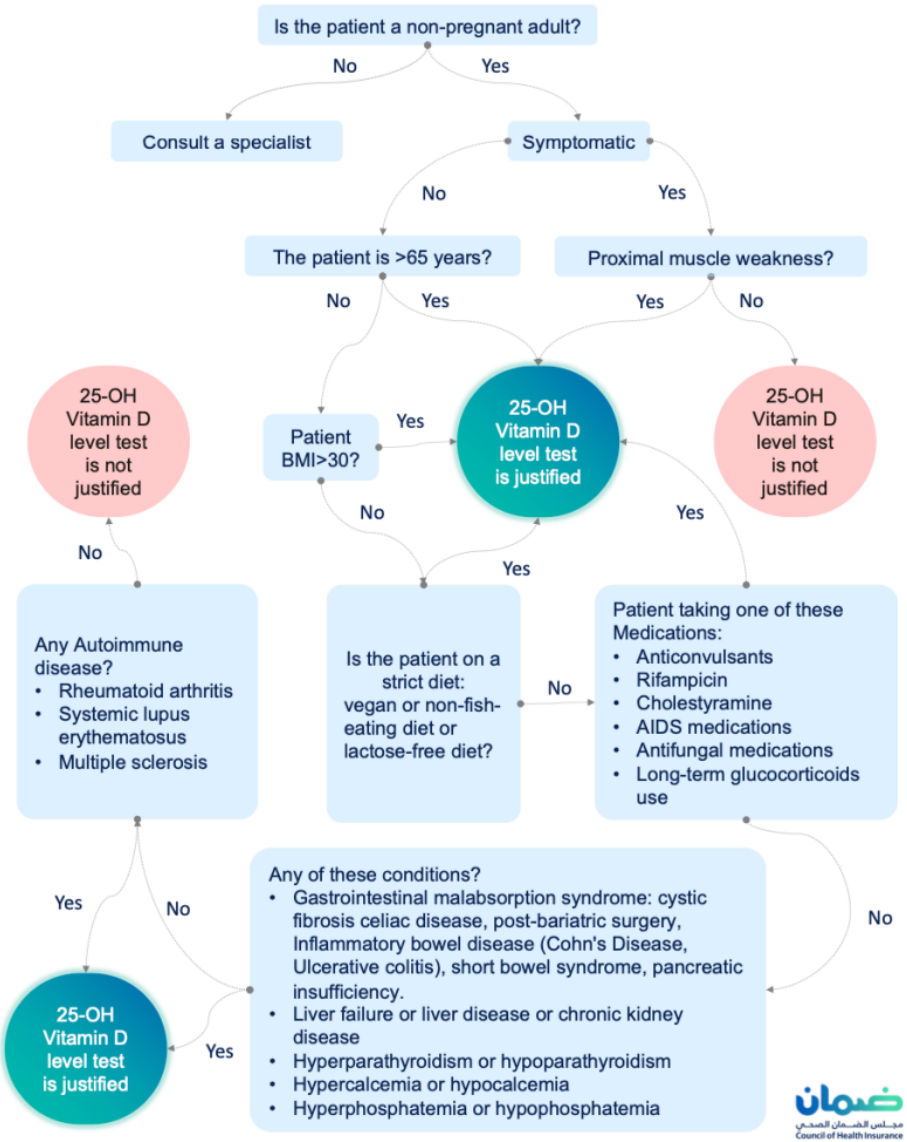

Figure 2. *CHI IDF Criteria for Insurance Coverage for Vitamin D Deficiency*

***Table 1**. Amended CHI Table on Vitamin D Supplementation, based on CHI Insurance Eligibility Criteria*

CHI has provided on its website (https://chi.gov.sa/Pages/default.aspx) a policy entitled **"Criteria for Insurance Coverage for Vitamin D Testing"**[1]. This policy lists the conditions where a Vitamin D test is justified and covered by CHI. According to CHI, the **eligible population for testing** are:

- Patients more than 65 years old.
- Symptomatic patients with proximal muscle weakness.
- Patient with a BMI>30.
- Patients on a strict diet (vegan, non-fish-eating diet, or lactose-free diet)
- Patients taking one of these medications:
    - Anticonvulsants
    - Rifampicin
    - Cholestyramine
    - AIDs medications
    - Antifungal medications
    - Long-term use of glucocorticoids.
- Patients with autoimmune disease:
    - Rheumatoid arthritis
    - Systemic lupus erythematosus
    - Multiple sclerosis.
- Patients with any of the following conditions:
    - Gastrointestinal malabsorption syndrome: cystic fibrosis celiac disease, post-bariatric surgery, inflammatory bowel disease (Crohn's disease, Ulcerative colitis), short bowel syndrome, pancreatic insufficiency
    - Liver failure or liver disease or chronic kidney disease
    - Hyperparathyroidism or hypoparathyroidism
    - Hypercalcemia or hypocalcemia
    - Hyperphosphatemia or hypophosphatemia.

After reviewing Lexicomp online database and the most updated guidelines on the management of Vitamin D

Deficiency, **the following definitions of Vitamin D insufficiency/deficiency** were provided from the *Vitamin D status correction in Saudi Arabia: an experts' consensus under the auspices of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO) (2017)*[2]:

- Most international institutions agree that individuals with **serum 25(OH)D levels below 50 nmol/l (20 ng/ml) require correction.**
- Local experts have established consensus on the following cutoffs based on their impact on bone health:
  - **Deficiency: Serum 25(OH)D < 50 nmol/l (<20 ng/ml).**
  - **Sufficiency: Serum 25(OH)D ≥ 50 nmol/l (≥20 ng/ml).**
- Adequacy for frail, osteoporotic elderly: Serum 25(OH)D > 75 nmol/l (>30 ng/ml).

The following dosing recommendations are provided for the two Vitamin D supplements that are SFDA-registered: **Cholecalciferol** and **Alfacalcidol**. The following table is provided by Lexicomp[3].

- Some experts suggest a range of 20 to 40 ng/mL (50 to 100 nmol/L) for most patients.
- The dose should be individualized based on patient-specific factors (e.g., presence of malabsorption, liver disease, kidney disease) and target 25(OH)D level. Calcium intake should also be ensured during therapy.

Indication	**Dosing (1mcg= 40 units)**
Cholecalciferol	
Vitamin D Insufficiency/ Deficiency Prevention **Adults**	**Oral:** 600 to 1,000 units (15 to 25 mcg) once daily
Vitamin D insufficiency/ Deficiency Treatment **Adults**	• **Serum 25(OH)D level <12 ng/mL (<30 nmol/L) or who are symptomatic (e.g., bone fracture/pain, muscle weakness)**, **or** in patients with concomitant **hypocalcemia: High-dose therapy: Initial dosing:** Oral: 50,000 units (1,250 mcg) once weekly (or equivalent dose administered once daily) for 6 to 12 weeks, then recheck 25(OH)D level; may repeat high-dose therapy if needed to achieve target 25(OH)D level. • **Serum 25(OH)D level 12 to <20 ng/mL (30 to <50 nmol/L) without symptoms or concomitant hypocalcemia: Low-dose therapy: Initial dosing:** Oral: 800 to 1,000 units (20 to 25 mcg) once daily for ~3 to 4 months; may adjust dose if needed every 3 to 4 months based on 25(OH)D level. Some experts suggest modest dose

	increases (e.g., to 2,000 units [50 mcg] once daily) if serum 25(OH)D levels have substantially increased but remain below target or switching to high-dose therapy if serum 25(OH)D levels remain substantially below target. • **Maintenance dosing:** Oral: Once target 25(OH)D level is achieved, continue at a maintenance dose of 600 to 2,000 units (15 to 50 mcg) once daily. **NOTE: Special populations (eg, obesity, patients on medications known to affect vitamin D metabolism, malabsorption, gastrectomy):** Higher doses or longer durations may be necessary for adequate replacement. In patients with malabsorption when target 25(OH)D levels cannot be maintained with cholecalciferol. **NOTE: No adjustments necessary in dosing for hepatic impairment, altered kidney function, hemodialysis, peritoneal dialysis, CRRT or PIRRT.**
Vitamin D deficiency, prevention **Pediatric** (Rickets Prevention)	• **Breastfed infants** (fully or partially): Oral: 400 units (10 mcg) daily beginning in the first few days of life; continue supplementation unless infant is transitioned to full formula intake. • **Children and Adolescents without adequate intake:** Oral: 600 units (15 mcg) daily. **NOTE:** Children with increased risk of vitamin D deficiency (chronic fat malabsorption, maintained on chronic antiseizure medications) may require higher doses; use laboratory testing [25(OH)D, PTH, bone mineral status] to evaluate.
Vitamin D deficiency (severe, symptomatic), Treatment **Pediatric**	• **Infants:** Oral: 2,000 units (50 mcg) daily for 6 weeks to achieve a serum 25(OH)D level >20 ng/mL; followed by a maintenance dose of 400 to 1,000 units (10 to 25 mcg) daily. **Note:** For patients at high risk of fractures a serum 25(OH)D level >30 ng/mL has been suggested. • **Children and Adolescents:** Oral: 2,000 units (50 mcg) daily for 6 to 8 weeks to achieve serum 25(OH)D level >20 ng/mL; followed by a maintenance dose of 600 to 1,000 units (15 to 25 mcg) daily. **Note:** For patients at high risk of fractures a serum 25(OH)D level >30 ng/mL has been suggested • Treatment should also include calcium supplementation.

	• **<u>NOTE:</u>** some patients with chronic fat malabsorption, obesity, or who are maintained on chronic antiseizure medications, glucocorticoids, HIV medications, or antifungals may require higher doses of cholecalciferol; monitor vitamin D status closely.
Vitamin D deficiency in cystic fibrosis, prevention, and treatment **Pediatric**	CF guidelines: • Recommended initial daily intake to maintain serum 25(OH)D level ≥30 ng/mL: o Infants: Oral: 400 to 500 units (10 to 12.5 mcg) once daily. o Children ≤10 years: Oral: 800 to 1,000 units (20 to 25 mcg) once daily. o Children >10 years and Adolescents: Oral: 800 to 2,000 units (20 to 50 mcg) once daily. • Dosing adjustment for serum 25(OH)D level between 20 to 30 ng/mL and patient adherence established (Step 1 increase): o Infants: Oral: 800 to 1,000 units (20 to 25 mcg) once daily. o Children ≤10 years: Oral: 1,600 to 3,000 units (40 to 75 mcg) once daily. o Children >10 years and Adolescents: Oral: 1,600 to 6,000 units (40 to 150 mcg) once daily. • Dosing adjustment for serum 25(OH)D level <20 ng/mL or persistently between 20 to 30 ng/mL and patient adherence established (Step 2 increase): o Infants: Oral: Increase up to a maximum 2,000 units (50 mcg) once daily. o Children ≤10 years: Oral: Increase to a maximum of 4,000 units (100 mcg) once daily. o Children >10 years and Adolescents: Oral: Increase to a maximum of 10,000 units (250 mcg) once daily.
	Alternate dosing: • Initial dose: Serum 25(OH)D level ≤30 ng/mL. o Infants: Oral: 8,000 units (200 mcg) once weekly. o Children and Adolescents: Oral: 800 units (20 mcg) once daily. • Medium-dose regimen: Serum 25(OH)D level remains ≤30 ng/mL and patient compliance established.

	○ Infants and Children <5 years: Oral: 12,000 units (300 mcg) once weekly for 12 weeks. ○ Children ≥5 years and Adolescents: Oral: 50,000 units (1,250 mcg) once weekly for 12 weeks. • High-dose regimen: Repeat 25(OH)D level remains ≤30 ng/mL and patient compliance established. ○ Infants and Children <5 years: Oral: 12,000 units (300 mcg) twice weekly for 12 weeks. ○ Children ≥5 years and Adolescents: Oral: 50,000 units (1,250 mcg) twice weekly for 12 weeks.
Vitamin D insufficiency or deficiency associated with CKD (stages 2 to 5, 5D), treatment; serum 25 hydroxyvitamin D [25(OH)D] level ≤30 ng/mL **Pediatric**	• Serum 25(OH)D level 16 to 30 ng/mL: Infants, Children, and Adolescents: Oral: 2,000 units (50 mcg) daily for 3 months or 50,000 units (1,250 mcg) every month for 3 months. • Serum 25(OH)D level 5 to 15 ng/mL: Infants, Children, and Adolescents: Oral: 4,000 units (100 mcg) daily for 12 weeks or 50,000 units (1,250 mcg) every other week for 12 weeks. • Serum 25(OH)D level <5 ng/mL: Infants, Children, and Adolescents: Oral: 8,000 units (200 mcg) daily for 4 weeks then 4,000 units (100 mcg) daily for 2 months for total therapy of 3 months or 50,000 units (1,250 mcg) weekly for 4 weeks followed by 50,000 units (1,250 mcg) 2 times/month for a total therapy of 3 months. • Maintenance dose [once repletion accomplished; serum 25(OH)D level >30 ng/mL]: Infants, Children, and Adolescents: Oral: 200 to 1,000 units (5 to 25 mcg) daily.

Nutritional rickets, treatment: Administer in combination with calcium supplementation	Daily therapy (preferred): • Infants: Oral: 2,000 units (50 mcg) daily for ≥3 months, followed by maintenance dose of 400 units (10 mcg) daily. • Children: Oral: 3,000 to 6,000 units (75 to 150 mcg) daily for ≥3 months, followed by maintenance dose of 600 units (15 mcg) daily. • Adolescents: Oral: 6,000 units (150 mcg) daily for ≥3 months, followed by maintenance dose of 600 units (15 mcg) daily.
	Single-dose therapy: • Infants ≥3 months: Oral: 50,000 units (1,250 mcg) once, or in divided doses over several days; after 3 months, initiate maintenance dose of 400 units (10 mcg) daily. • Children: Oral: 150,000 units (3,750 mcg) once, or in divided doses over several days; after 3 months, initiate maintenance dose of 600 units (15 mcg) daily. • Adolescents: Oral: 300,000 units (7,500 mcg) once, or in divided doses over several days; after 3 months, initiate maintenance dose of 600 units (15 mcg) daily.
Alfacalcidol	
Chronic kidney disease-mineral and bone disorder (hypocalcemia, secondary hyperparathyroidism, or osteodystrophy): **Adults:**	Note: Kidney Disease: Improving Global Outcomes (KDIGO) guidelines do not recommend routine use of vitamin D analogs in patients not on dialysis with chronic kidney disease (CKD) stages G3 to G5; it is reasonable to reserve use for patients with CKD stages G4 or G5 and with severe and progressive hyperparathyroidism. Caution is advised to avoid hypercalcemia or elevated phosphate levels (KDIGO 2017). • **Patients with moderate to severe chronic kidney disease not yet on dialysis:** Note: The magnitude of parathyroid hormone (PTH) response is highly variable. KDIGO guidelines recommend initiating with low doses independent of initial PTH concentration and then titrating based on PTH response while avoiding hypercalcemia (KDIGO 2017). ○ **Oral: Initial**: 0.25 mcg once daily (manufacturer's labeling); however, lower doses have been reported (eg, 0.25 mcg 3 times weekly) (Reichel 2010); may

	titrate dose upward in increments of 0.25 mcg/day every 2 months (maximum dose: 1 mcg/day). • **Patients on dialysis**: ○ **Oral**: Initiate carefully; 0.25 mcg once daily is the lowest recommended dose in the manufacturer's labeling and has been reported elsewhere (Naves-Díaz 2008; Ogawa 2012; Shoji 2004; manufacturer's labeling). If necessary, may titrate dose upward in increments of 0.25 to 0.5 mcg/day every 2 to 4 weeks (maximum dose: 3 mcg/day). ○ **IV**: Initiate carefully; 0.5 mcg 3 times weekly is the lowest recommended dose in the manufacturer's labeling. If inadequate response, may titrate dose upward in increments of 0.5 to 1 mcg per dialysis (maximum dose: 12 mcg/week).
Hypoparathyroidism, chronic **Adults**	• **Oral: Initial (low end of range)**: 0.5 mcg/day; may adjust dose carefully in increments of 0.25 to 0.5 mcg/day not more frequently than every 2 to 3 days to achieve desired calcium levels while avoiding hypercalcemia. Usual range: 0.5 to 4 mcg/day. • Patients discontinuing recombinant PTH therapy: Significantly increased doses of alfacalcidol and supplemental calcium may be acutely required to prevent severe hypocalcemia, especially if recombinant PTH therapy is discontinued abruptly; consider using alfacalcidol (and supplemental calcium) at higher doses than the pre-rPTH treatment doses, with careful monitoring of calcium levels.
Hyperparathyroidism (primary or tertiary), rickets/osteomalacia: **Adults**	• **IV, Oral: Initial**: 1 mcg once daily; if needed, may titrate upward in weekly increments of 0.25 to 0.5 mcg (usual effective dose: 1 to 3 mcg/day) using caution to avoid hypercalcemia. • Following initial response, maintenance doses of 0.25 to 1 mcg/day may be sufficient depending on condition being treated. • If hypercalcemia occurs, interrupt therapy until plasma calcium returns to normal, then restart at a reduced dose (eg, 50% of previous dose).
Osteoporosis: **Adults**	**IV, Oral: 0.5 to 1 mcg/day.**
NOTE: No dosage adjustments recommended in hepatic impairment or altered kidney function.	

Chronic kidney disease-mineral and bone disorder (hypocalcemia, secondary hyperparathyroidism, or osteodystrophy), hyperparathyroidism (primary or tertiary), hypoparathyroidism, rickets/osteomalacia: **Pediatrics:**	• **Neonates and premature infants**: IV, Oral: Initial: 0.05 to 0.1 mcg/kg/day. Adjust dose according to clinical response using caution to avoid hypercalcemia. **Note**: If administering oral drops, half-drop doses should be rounded up to the next whole number of drops. • **Infants and Children <20 kg**: IV, Oral: Initial: 0.05 mcg/kg/day. Adjust dose according to clinical response using caution to avoid hypercalcemia. **Note**: If administering oral drops, half-drop doses should be rounded up to the next whole number of drops. • **Children and Adolescents ≥20 kg**: IV, Oral: Initial: 1 mcg once daily; if needed, may titrate upward in weekly increments of 0.25 to 0.5 mcg using caution to avoid hypercalcemia. Following initial response, maintenance doses of 0.25 to 1 mcg/day may be sufficient depending on condition being treated. • If hypercalcemia occurs, interrupt therapy until plasma calcium returns to normal, then restart at a reduced dose (eg, 50% of previous dose).
Neonatal hypocalcemia	**Neonates and premature infants: IV, Oral:** Initial: 0.05 to 0.1 mcg/kg/day; up to 2 mcg/kg/day may be necessary. Note: If administering oral drops, half-drop doses should be rounded up to the next whole number of drops.
Osteoporosis	**Infants, Children, and Adolescents:** Oral (tablets): 0.01 to 0.03 mcg/kg/day

For the full level of evidence, please refer to the full report.