UNC MEDICAL CENTER GUIDELINE

High-Dose Vitamin D_3 (Stoss Therapy) Use in Cystic Fibrosis Patients

This guideline is intended to review Stoss therapy's clinical use, dosing regimen, and monitoring parameters. This information is intended to help clinician's identify therapeutic considerations regarding the use of high-dose Vitamin D_3 in patients with cystic fibrosis (CF).

BACKGROUND

Low vitamin D levels are common in individuals with CF despite supplementation which is of concern because of the potential for chronic bone pain, chest deformity, and vertebral fractures, along with its immunomodulatory effects on lung inflammation and pulmonary function. The US CF Foundation currently recommends a target 25-hydroxyvitamin D (25-OHD) level of ≥30 ng/mL (75 nmol/L). Furthermore, the CF Foundation recommends that individuals with CF be treated with supplemental vitamin D3 (cholecalciferol) to maintain adequate vitamin D levels.[1] Single high-dose vitamin D3 replacement therapy, known as Stoss therapy has been demonstrated to be safe and effective in both pediatric and adult individuals with CF.[2-3]

A retrospective review by Shepherd et al[2] investigated the safety and efficacy of a single oral high-dose vitamin D3 in pediatric CF patients, dosed based on the patient's age and baseline 25-OHD serum level. Maintenance oral vitamin D3 supplementation of 400 IU daily (for patients under one year of age) to 800 IU daily (those older than one year) was given to patients. The 42 patients who received Stoss therapy had a statistically significant increase in mean 25-OHD level at all study time points compared to baseline, whereas 82.4% of the control group remained vitamin D deficient with an overall increase of 2 ng/mL. Additionally, values at 1 month and combined 3-6 months remained above the target level of 30 ng/mL (mean increase by 12.8 ng/mL in 3 months) with no evidence of vitamin D toxicity including hypercalcemia, hyperphosphatemia, nausea, or renal calculi.[2]

With the demonstrated efficacy of Stoss dosing in pediatric patients with CF, a prospective study evaluated high-dose cholecalciferol in adult patients with CF and pancreatic insufficiency. Patients with baseline serum 25-OHD levels <30 ng/mL or <20 ng/mL received 300,000 IU or 500,000 IU, respectively, and were re-dosed at month 6 if their 3 month serum levels were <45 ng/mL. Patients did not receive any additional daily vitamin D supplementation but were instructed to continue taking CF multivitamin.[3] Mean 25-OHD levels increased by 13.78 ng/ml from mean baseline levels at 9 months following Stoss therapy. The difference in 25-OHD levels was significant between baseline and months 3 and 9. There were no levels at or above the upper limit of normal of 50 ng/mL, calcium levels were either below or within normal limits, and no adverse effects were reported.[3]

Stoss therapy has the potential to improve serum 25-OHD target level attainment over 3 to 6 months with a one-time single oral dose of vitamin D. With the high pill burden associated with CF, eliminating the need for additional Vitamin D supplementation beyond the multivitamin can help mitigate poor compliance.[2-3]

PATIENT CONSIDERATIONS

Consider use of high dose vitamin D3 or Stoss therapy in children 2 years or older with either of the following clinical scenarios:

- Cystic fibrosis with pancreatic insufficiency who failed 6 months of maximum recommended daily dose of maintenance vitamin D3 based on the CF Foundation guidelines:
  - > 12 months to less than 10 years: 4000 IU per day
  - ≥ 10 years: 10,000 IU per day

OR

- Patients with a history of poor adherence and a 25-OHD level <30 ng/mL

Avoid Stoss therapy in the following scenarios:

- 25-OHD serum level ≥ 30 ng/mL
- Corrected calcium > 10.5 mg/dl (or ionized calcium higher than 5.4 mg/mL)

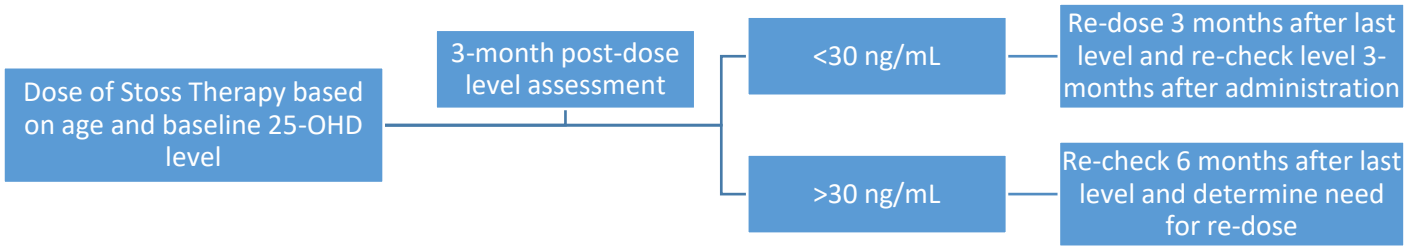
DOSING

Patients are required to have a baseline serum 25-OHD level within the last 6 months prior to starting therapy to determine the appropriate dosage based on level and age. Patients should continue their prior home daily CF multivitamin post-Stoss administration**.**

Table 1. Stoss Therapy Dosing based on patient's age and 25-OHD levels

Serum 25-OHD level (ng/mL)	<3 years	3-12 years	>12 years
<10	200,000 IU	400,000 IU	600,000 IU
10-20	150,000 IU	350,000 IU	500,000 IU
20-30	100,000 IU	200,000 IU	300,000 IU

Figure 1. Follow up monitoring post-Stoss administration



- Re-dose with the same dose given initially, 3 months after level assessment based on Figure 1 (above) and if calcium and phosphate levels are normal and there are no signs of vitamin D toxicity (such as hypervitaminosis D, hypercalcemia, hyperphosphatemia, nausea, and renal calculi).
- See 'Dosage Form Considerations' below for various administrations methods.
- If a patient's level remains <30 ng/mL despite two doses of Stoss therapy, consider **Pediatric Endocrinology Consult.**

MONITORING

Potential risks of high-dose cholecalciferol may include hypervitaminosis D, hypercalcemia, hyperphosphatemia, nausea, and renal calculi. While the risk of this is low, it should still be monitored closely.

Table 2. Monitoring Recommendations for High-Dose Vitamin D3[1,4]

Laboratory Parameters	Frequency
Serum 25-OHD level	At 3 months after any high-dose administration or after any dose adjustment until at goal
Calcium	
Phosphorus	
Albumin	

DOSAGE FORMS CONSIDERATIONS

- Patients **able** to swallow tablets whole:
  - Give total dose by mouth using **Vitamin D3 (cholecalciferol) 50,000 unit** tablets
- Patients **unable** to swallow whole tablets:
  - Crush Vitamin D3 (cholecalciferol) 50,000 unit tablets and give in pudding or apple sauce

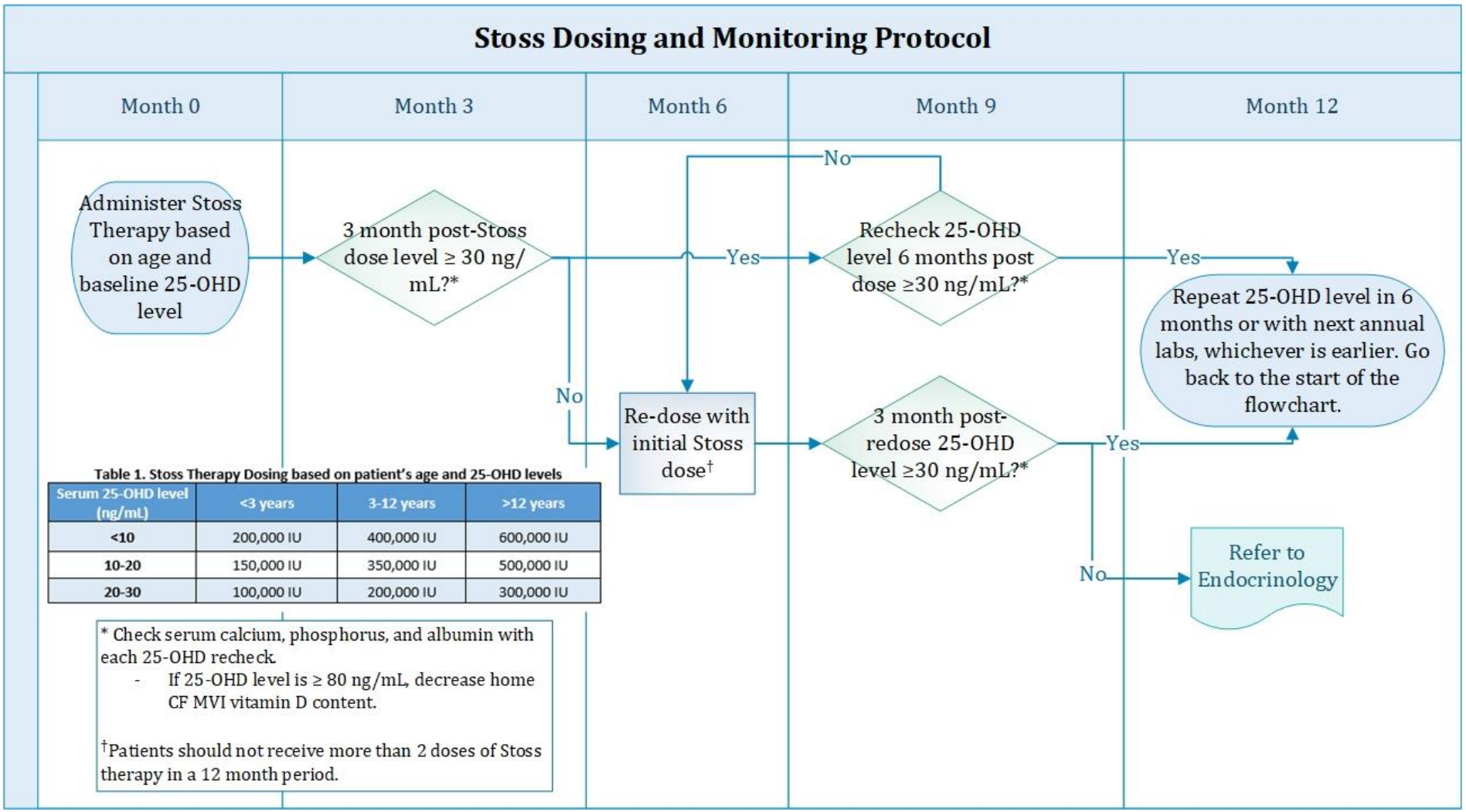
THERAPY CONSIDERATIONS

- Due to being fat soluble, ideally administer Stoss dose in clinic with high-fat snack along with pancreatic enzyme therapy to enhance absorption.[4]
- Do not administer more frequently than every 6 months. There is no literature supporting more frequent dosing of Stoss therapy, including quarterly dosing. [2-3]
  - If 25-OHD level remains <30 ng/mL after 2 doses of Stoss therapy along with maintenance therapy, consult **Pediatric Endocrinology** for further management and work-up.
- Counsel and monitor for signs of vitamin D toxicity, including: nausea, vomiting, constipation, fatigue, irritability, weakness, and confusion.[4]

REFERENCES

1. Tangpricha V, Kelly A, Stephenson A, et al for the Cystic Fibrosis Foundation Vitamin D Evidence-Based Review Committee. An Update on the Screening, Diagnosis, Management and Treatment of Vitamin D Deficiency in Individuals with Cystic Fibrosis: Evidence-Based Recommendations from the Cystic Fibrosis Foundation. *J Clin Endocrinol Metab.* 2012; 97(4):1082-1093.
2. Shepherd D, Belessis Y, Katz T, et al. Single high-dose vitamin D3 (stoss) therapy – a solution to vitamin D deficiency in children with cystic fibrosis? *J Cyst Fibrosis.* 2013; 13: 177–82.
3. Janzen KM, Sakon C, Lehman A, et al. High-dose Cholecalciferol Supplementation in Adults with Cystic Fibrosis. *Pharmacotherapy*. 2019; 39(9): 874-880.
4. Cholecalciferol. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed January 14, 2021.

Stoss Dosing and Monitoring Protocol



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* Check serum calcium, phosphorus, and albumin with each 25-OHD recheck.

- If 25-OHD level is ≥ 80 ng/mL, decrease home CF MVI vitamin D content.

†Patients should not receive more than 2 doses of Stoss therapy in a 12 month period.