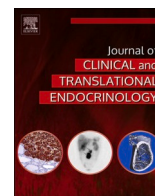


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## A Clinician's guide to vitamin D supplementation for patients with cystic fibrosis

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## ABSTRACT

Vitamin D deficiency is common in the general population, and even more so in patients with cystic fibrosis. Deficiency is exacerbated in cystic fibrosis patients because of a myriad of causes including malabsorption, decreased fat mass, reduced 25-hydroxylation of vitamin D, reduced exposure to sunlight, decreased vitamin D binding protein, and exposure to drugs that increase catabolism. In turn, vitamin D deficiency can contribute to poor bone health. Additionally, it may contribute to pulmonary decline in the form of worsening pulmonary function, increased colonization with pathogens, and increased pulmonary exacerbation. Because vitamin D deficiency is correlated with negative clinical effects in multiple organ systems of patients with cystic fibrosis, it is important to screen for and treat deficiency in these patients. The Cystic Fibrosis Foundation has issued guidelines for the treatment of vitamin D deficiency, targeting serum levels of 25-hydroxyvitamin D of at least 30 ng/ml. The guidelines offer age-specific escalating dose regimens depending on serum vitamin D levels, with monitoring at 12-week intervals after changing therapy. They address the literature on alternative vitamin D sources, such as UV lamps, ideal formulations (cholecalciferol in preference to ergocalciferol), and optimal vehicles of administration. Despite these detailed recommendations, most centers are still unable to achieve in-target serum vitamin D levels for many of their patients. Future research examining ideal treatment regimens to achieve serum targets and maximize clinical effects are needed. Moreover, it is unknown whether vitamin D sufficiency will be easier to achieve on new triple therapy cystic fibrosis drug combinations, and how these drugs will contribute to vitamin D-related clinical outcomes.

## Introduction

Cystic fibrosis (CF) is an autosomal recessive disease resulting from a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Cystic fibrosis affects multiple organ systems including the lungs, the exocrine and endocrine pancreas, and the gastrointestinal tract. Pancreatic insufficiency, which occurs in 90% of patients with cystic fibrosis, and a multitude of other cystic fibrosis-related factors cause these patients to be at increased risk of fat malabsorption and deficiency of fat-soluble vitamins. Despite patients being provided oral

supplementation, the prevalence of vitamin D insufficiency has been noted to be as high as 90% at cystic fibrosis centers [1]. Even when treatment is given with vitamin D supplementation according to the current Cystic Fibrosis Foundation guidelines, many patients are unable to achieve a state of vitamin D sufficiency (>30 ng/ml) [2]. When compared to healthy controls, children with cystic fibrosis are more commonly vitamin D deficient (<20 ng/ml) or insufficient (20–30 ng/ml) [3], even when seasonality and supplementation are considered [1].

Vitamin D is important for bone, immunologic, gastrointestinal, and pulmonary health [4–6]. The degree to which vitamin D makes a direct

**Abbreviations:** 25(OH)D, 25-hydroxyvitamin D; CFTR, cystic fibrosis transmembrane conductance regulator; D2, ergocalciferol; D3, cholecalciferol; BMD, bone mineral density; CF, cystic fibrosis; PTH, parathyroid hormone; NTM, nontuberculous mycobacteria; RTC, randomized control trial; CFRD, cystic fibrosis-related diabetes.

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**Table 1**  
Risk Factors for Vitamin D Deficiency.

| Decreased intake/<br>Production   | Decreased Absorption/<br>Storage       | Increased catabolism/<br>Excretion             |
|---|--|--|
| Decreased Vitamin D-<br>Fortified Foods   | Pancreatic Exocrine<br>Insufficiency   | Glucocorticoids                                |
| Inadequate<br>Supplementation   | Decreased Sun Exposure                 | Select Antimicrobials<br>(rifampin, isoniazid) |
| Decreased Sun Exposure<br>• High Latitude<br>• Sunblock Use<br>• Melanin Content of<br>Skin | Decreased Vitamin D<br>Binding Protein |  |
|   | Decreased 25-<br>hydroxylation         |  |
|   | Decreased Body Fat                     |  |

clinical impact on organ health outside of the musculoskeletal system is unknown. It is also unclear whether improved clinical health is achieved at a defined serum 25-hydroxyvitamin D value, or if improved health is on a continuum according to serum vitamin D concentrations. It may be that achieving sufficiency at an earlier age and prior to organ system decline is more clinically significant than treatment later in the disease course. Also unknown is whether different organ systems might benefit at differing levels of vitamin D sufficiency or with differing treatment regimens. In recent literature, the effects of vitamin D deficiency on extra-skeletal organ systems in patients with cystic fibrosis have been more specifically examined. Systems of interest include the pulmonary system, immune system, gastrointestinal system, and the endocrine system, as these have been widely known to be compromised in cystic fibrosis patients. Moreover, disease of these organ systems contributes significantly to morbidity and mortality of patients with cystic fibrosis. We present here a case of vitamin D deficiency in a patient with cystic fibrosis to prompt discussion about metabolism of vitamin D in the cystic fibrosis population:

The patient is a 12 year old female with cystic fibrosis who carries two copies of the F508del mutation, who presented with a 25-hydroxyvitamin D level of 8 ng/ml during her yearly labs. She has a history of cystic fibrosis-related pancreatic insufficiency and was diagnosed with cystic fibrosis-related diabetes one year ago when her oral glucose tolerance test resulted a fasting blood glucose of 92 mg/dl and a two hour blood glucose of 209 mg/dl with a corresponding A1C of 6.6%. She has been maintained on 6 units of daily detemir insulin since that time with an A1C of 5.8% on her most recent lab set. She has been hospitalized with pulmonary endobronchitis twice and has colonization with *Pseudomonas aeruginosa*. Her most recent hospitalization was six months previous. She has baseline FEV1 percentages near 90%, but during her previous hospitalization it had dropped to 70%, and since has rebounded. She is mid- to late-pubertal, but not yet menstrual. She has never suffered a broken bone. She is not extremely active, and prefers indoor activities. She maintains a typical cystic fibrosis dietary prescription rich in proteins and fats, and has a body mass index at the 25%. She is intermittently compliant with her overall cystic fibrosis care, including taking her enzymes and vitamin D supplementation. Vitamin

**Table 2**  
Vitamin D deficiency effects by system.

| Musculoskeletal  | Pulmonary                           | Immunology   | Gastrointestinal                              | Endocrine                                 |
|--|-------------------------------------|--|---|---|
| Impaired bone mineralization   | Decreased pulmonary<br>function     | Shift away from innate immunity                    | Decreased integrity of the<br>mucosal barrier | Increased CFRD                            |
| Elevated PTH   | Colonization with<br>pathogens      | Shift towards adaptive immunity                    | Shift towards less beneficial<br>microbiota   | Increase in impaired glucose<br>tolerance |
| Decreased long term bone mass<br>accrual                                       | Increased pulmonary<br>exacerbation | Increased inflammation and perhaps<br>autoimmunity |   | Decreased insulin sensitivity             |
| Lower adult bone mass<br>Increased progression to osteoporosis<br>and fracture |                                     |  |   | Decreased insulin secretion               |

D is prescribed as ADEKs with an additional 1000 IU/day of cholecalciferol. Next week, she will start on highly effective modulator therapy (elexacaftor/tezacaftor/ivacaftor).

Concern was raised about her very low vitamin D level, so 50,000 IU/day of cholecalciferol with a powder-based vehicle once per week was started, along with calcium carbonate 500 mg (200 mg of elemental calcium) twice daily with meals. A baseline DEXA scan was obtained with a Z-score at the hip of  $-1.0$  and at the spine of  $-1.2$ . Compliance with enzymes and medication administration was encouraged. A repeat 25-hydroxyvitamin D level twelve weeks after starting supplementation was 32 ng/ml. The patient was then placed on maintenance dosing of 2000 IU/day of vitamin D3.

This case presents 3 main questions:

- What are the risk factors that make patients with cystic fibrosis uniquely susceptible to vitamin D deficiency?
  - How is vitamin D deficiency potentially involved in multiorgan system disease in patients with cystic fibrosis?
  - How can vitamin D sufficiency be best achieved in this population?
- 1) What are the risk factors that make patients with cystic fibrosis uniquely susceptible to vitamin D deficiency? (Table 1)

Vitamin D insufficiency and deficiency are known to be quite common in the general population and occur even more commonly in the cystic fibrosis population [5]. The Cystic Fibrosis Foundation guidelines and Endocrine Society guidelines for care both recommend maintaining 25-hydroxyvitamin D (25(OH)D) levels of  $>30$  ng/ml [7,8]. Comparing the degree of vitamin D deficiency in the cystic fibrosis population with controls can be difficult, since seasonal variation in serum vitamin D levels are well documented [9]. Many studies do not standardize or control for seasonal variation. Moreover, compliance with pancreatic enzymes and adherence to vitamin D supplementation regimens using ergocalciferol (D2) or cholecalciferol (D3) can acutely affect 25-hydroxyvitamin D levels.

There are factors in the cystic fibrosis population that can exacerbate vitamin D deficiency in excess compared to the general population. To begin, fat malabsorption is experienced by patients with cystic fibrosis due to pancreatic insufficiency. Even with pancreatic enzyme supplementation, absorption may be decreased [10] and noncompliance with medications and poor dietary habits can exacerbate the problem. Other sources of vitamin D may be limited as well. One study found that sunlight exposure was the most predictive factor of vitamin D status prior to pulmonary exacerbation [11]. Some hypothesize that patients with CF avoid sunlight exposure due to photosensitivity from antibiotics [12,13]. Many patients with cystic fibrosis are underweight, and the decreased body fat may store less vitamin D than in those with healthy body weight [13]. Additionally, poor hepatic 25-hydroxylation of vitamin D and accelerated enterohepatic dumping can decrease overall vitamin D stores [10,14]. Patients with CF may have decreased storage of vitamin D because of decreased levels of vitamin D binding protein, which is the main carrier in circulation and helps recover 25-hydroxyvitamin D excreted in urine [15]. Finally, people with cystic fibrosis may experience increased catabolism of vitamin D due to exposure to

glucocorticoids, rifampin, and isoniazid [16,17].

2) How is vitamin D deficiency potentially involved in multisystem organ disease in patients with cystic fibrosis? (Table 2).

### Bone

Historically, vitamin D deficiency has been examined in the context of its effect on bone health and risk of fracture. Low bone mineral density (BMD) may result in vertebral fractures. In turn, fractures can compromise lung function, quality of life, and possible ability for lung transplantation. Bone mineral content decreases with time in individuals with CF. When low bone density is defined as an age-adjusted Z-score of less than  $-2$ , the prevalence of low BMD is estimated at 9 to 38% in children and adolescents [18]. Additionally, 24% of adults experience osteoporosis as defined as T-score  $< -2.5$  and 38% have osteopenia (T-score  $-1$  to  $-2.5$ ), with incidence of both increasing with age [19]. In one study by Henderson and Madsen, the mean Z-scores (standardized for age) for the lumbar spine were  $< 0$  for children aged 5–18 years [20]. These results showed that osteopenia may occur even in the first decade of life in patients with cystic fibrosis and that bone loss accelerates during adolescence and early adulthood.

Increased life expectancy in CF requires a greater need to monitor for CF-related low bone mineral mass. Risk factors for low bone mass include pancreatic insufficiency, vitamin D and K insufficiency, gastrointestinal calcium loss, CFRD, glucocorticoids, chronic inflammation, reduced sex hormones, and reduced growth hormone [21]. Additionally, CFTR dysfunction in bone resulting in abnormalities in bone turnover plays a role in CF-related bone disease [22].

The high prevalence of vitamin D insufficiency/deficiency in CF is well documented as a significant risk factor for low BMD [13]. However, the role of parathyroid hormone (PTH) is often overlooked. Low vitamin D status leads to elevations in PTH termed secondary hyperparathyroidism. Biochemically, the increase in PTH to maintain calcium homeostasis occurs at the expense of bone demineralization and potentially increased risk of fracture [23]. Variations in the PTH thresholds exist to define hyperparathyroidism and studies suggest that a combined assessment of 25-hydroxyvitamin D levels and PTH are needed to fully assess the risk of compromised bone health [24].

The Cystic Fibrosis Foundation recommends treating serum 25-hydroxyvitamin D levels to 30 ng/ml [7]. PTH levels have been shown to correlate inversely with serum 25-hydroxyvitamin D levels until 30–40 ng/ml [3]. Additionally, a study that examined 675 post-mortem subjects with iliac crest biopsy and vitamin D levels found that no patients with 25-hydroxyvitamin D levels over 30 ng/ml experienced pathologic osteoid development on bone biopsy [25]. Maintaining sufficient levels of vitamin D likely is bone protective.

### Pulmonary

There is much interest as to whether vitamin D sufficiency can improve pulmonary health in patients with cystic fibrosis, but results are conflicting. Bacterial colonization, pulmonary function, and frequency of exacerbation have all been studied as clinical endpoints to vitamin D treatment. Firstly, patients with vitamin D insufficiency are at risk of pulmonary infection with pathogens that can accelerate lung function decline, such as nontuberculous mycobacteria (NTM) and *Pseudomonas aeruginosa*. Vitamin D is thought to have a role in the immune response to these infections, and sufficiency has been associated with fewer positive NTM cultures and decreased pulmonary inflammation in association with *P. aeruginosa* infection [26,27]. In addition, in healthy lungs the bronchial epithelia are capable of 1-alpha hydroxylation of 25(OH) D. However, cystic fibrosis bronchial epithelial cells may have an impaired ability to activate 25-hydroxyvitamin D to its active form, 1,25-dihydroxyvitamin D, which may partially explain the increased

susceptibility to infection and proinflammatory shift in CF [28]. For that reason, it has been hypothesized by some that calcitriol may be a more effective medication than cholecalciferol in enhancing pulmonary outcomes [29]. Second, several studies have looked at vitamin D status and its association with pulmonary function and exacerbations in patients with cystic fibrosis. In children, vitamin D deficiency is associated with higher rates of pulmonary exacerbation, bacterial colonization, and pulmonary function [2,30–34]. Conversely, there have been publications that have not substantiated the pulmonary benefits of vitamin D supplementation in young children and adults [35,36]. Because of its immune-modulation effects, it has been postulated that high dose vitamin D given during pulmonary exacerbation may improve lung functions and decrease risk of further exacerbations. The Vitamin D for Enhancing the Immune System in Cystic Fibrosis (DISC) trial was a multicenter, double-blind randomized control trial (RCT) that administered 250,000 IU vitamin D3 to adults with CF during pulmonary exacerbation, followed with a maintenance dose of vitamin D3. However, the DISC study did not find differences in time to next pulmonary exacerbation and rehospitalization, improved survival, or lung function despite a verified rise in mean 25-hydroxyvitamin D levels [37]. The discordant results between studies examining pulmonary health may have occurred for a variety of reasons. Firstly, the relationship between vitamin D levels and health may be an association rather than causative, since patients who consistently take vitamin D may also be more consistent with pulmonary toilet and other health care tasks. Additionally, a difference in outcomes may seem more extreme because of the paucity of RCT to be examined. Also, in studies with patients who start with higher vitamin D levels, a threshold for improvement may be present that is unable to be detected. Finally, maintaining lifelong vitamin D sufficiency may be more important in terms of preventing decline than is correction of vitamin D deficiency once it has already occurred.

### Gastrointestinal

Gut microbiota may contribute to the multi-organ systemic health of patients with cystic fibrosis. In a 2018 RCT, 23 vitamin D insufficient patients were randomized to 50,000 IU weekly vitamin D3 or placebo for 12 weeks. More pathogenic species of gut microbiota (taxa *Gammmaproteobacteria*) existed in those who were vitamin D insufficient ( $< 30$  ng/ml). Conversely, those treated with vitamin D had a shift towards microbiota that were potentially beneficial (*Bacteroidia* class) [38]. In addition to altering the make-up of microbiota, evidence from murine and human studies display the ability of vitamin D to maintain integrity of gut mucosal barrier and to reduce inflammation in cells that are CFTR knockouts [39,40]. Vitamin D may enhance intercellular junctions and reduction of pro-inflammatory cytokines like IL 8, ultimately improving gastrointestinal health [40].

### Endocrine

Vitamin D plays a regulatory role in insulin secretion, beta cell survival, and calcium flux within beta cells. Previous studies have shown that vitamin D deficiency impaired glucose-mediated insulin secretion and pancreatic beta cells in rodents [41–44], while vitamin D supplementation seems to restore such glucose stimulated insulin secretion [41,45]. Furthermore, vitamin D has a direct effect on beta cell function by regulation of vitamin D responsive genes found on pancreatic beta cells [46,47] and by regulating extracellular calcium concentration and flux through the beta cell [48]. Insulin secretion is a calcium dependent process [49]; alterations in calcium flux can affect insulin secretion [50–52]. Previous studies have shown that vitamin D deficiency plays a role in the pathophysiology of diabetes, suggesting that vitamin D deficiency is an important environmental factor for development of the disease. In type 1 diabetes, vitamin D has been suggested to act via its immunomodulatory effects by promoting a shift from a Th1 to a Th2

cytokine, enhancing the clearance of auto-reactive T cells and decreasing the Th1 cell infiltration within the pancreatic islets. This reduces cytokine-induced beta cell damage and may preserve beta cell mass [53,54]. In type 2 diabetes, vitamin D increases insulin secretion and improves peripheral insulin sensitivity [55,56]. Cystic fibrosis-related diabetes (CFRD) is a unique form of diabetes, characterized primarily by insulin deficiency and secondarily by insulin resistance [57,58]. Oxidative stress, inflammation, and beta cell dysfunction are risk factors for CFRD [59]. Given the immunomodulatory properties of vitamin D and its effect on insulin secretion and beta cell function, vitamin D may play a regulatory role in CFRD. Although vitamin D deficiency has been well documented in CF, studies investigating the role of vitamin D on the progression of impaired glucose tolerance to CFRD have been limited and provide conflicting results. Pincikova, et al assessed the relationship between vitamin D status and cystic fibrosis-related glucose intolerance in a Scandinavian population. Their data showed that the degree of vitamin D insufficiency was a significant risk factor for CFRD after controlling for pulmonary and pancreatic function, liver dysfunction, and exposure to steroids [60]. Furthermore, patients with impaired glucose tolerance had lower vitamin D levels than patients with normal glucose tolerance. This suggests that improving vitamin D status in cystic fibrosis patients may be protective against the progression to CFRD. The positive effect of vitamin D supplementation may be most beneficial during childhood while the beta cell mass is largely intact with preserved insulin secretion and greater peripheral insulin sensitivity. As insulin production decreases over time due to exocrine pancreatic fibrosis and chronic beta cell stress, effect of vitamin D becomes less profound. Coriati, et al investigated the relationship between vitamin D levels and glucose tolerance in an adult population with CF and found no association between vitamin D and glucose metabolism, insulin secretion, or insulin resistance indices [61]. A possible explanation for the lack of association between vitamin D status and glucose metabolism in this study as compared to the positive association found in the Pincikova study is that the proportion of vitamin D deficiency was far lower in the Coriati study population, with 42.1% of patients having 25-hydroxyvitamin D levels >30 ng/ml, whereas the Pincikova study had only 16% of patients with 25(OH)D over 30 ng/ml [60]. Thus far there are no published trials specifically designed to investigate whether long-term vitamin D supplementation reduces the risk of developing CFRD. Firm conclusions cannot be drawn at this time regarding the protective effect of vitamin D sufficiency on CFRD.

### 3) How can vitamin D sufficiency be best achieved in this population?

The clinician should consider several factors when supplementing vitamin D in adults and children with CF. These include the formulation, route, vehicle substance, and the timing, dose and duration of treatment.

In regards to formulation of supplemented vitamin D, cholecalciferol is preferred by the Cystic Fibrosis Foundation guidelines. When supplementation of vitamin D is given orally, it can be administered as ergocalciferol (D2) or cholecalciferol (D3). Based on several studies that posited that ergocalciferol is less readily absorbed than cholecalciferol in patients with cystic fibrosis [10,62], cholecalciferol is now the preferred formulation. However, ergocalciferol seems to be sufficient if given at higher doses. When vitamin D3 was given at 50,000 IU per week versus Vitamin D2 at 50,000 IU twice weekly to children over an 8 week time period, similar rates of sufficiency were achieved, although only two thirds of either group achieved states of sufficiency [63]. Whether one formulation or the other has more clinical effect on other organ systems is unknown. A study of 16 patients showed that vitamin D status and treatment with ergo- or cholecalciferol were associated with decreased markers of inflammation in a dose-dependent manner, although vitamin D2 doses were nearly double the D3 doses required to achieve sufficiency [64]. Interestingly calcitriol has been understudied as a possible vehicle for vitamin D replacement, although there is evidence indicating it may be more effective in enhancing pulmonary health than

ergocalciferol or cholecalciferol [29]. Limiting the use of calcitriol are its short half life and its risk of hypercalcemia.

In addition to dietary intake and supplementation, sunlight or sun beds may offer an alternative route to oral treatment. There have been questions as to whether patients are as adherent to UVB therapy as they are to oral supplementation [62]. While UVB light may be effective [65], it may be more equivalent to supplementation with D2 than with D3 [62]. There are no studies associating skin cancer with UVB light in patients with cystic fibrosis, but in the general population there are studies linking UVB to skin cancer, immune suppression, and oxidative stress [66]. Optimal time of exposure and area of skin exposure are only estimated and are likely affected by skin tone and by the latitude at which the exposure occurs. Some reviews have suggested increasing exposure to sunlight without sun block lotion, and keeping exposure time limited to avoid sunburn. Other authors recommend exposure 2–3 times per week in warm seasons [12,13,67]. In the general population, it is thought that 30 minutes of full body exposure to the sun at high latitude in light skinned people, or 20 minutes in a sun bed, would produce the equivalent of 10,000–20,000 IU of vitamin D [68]. Side effects like skin erythema and increased photosensitivity on some medications may be a deterrent to this treatment [65,69]. The 2012 CFF guidelines for vitamin D deficiency did not recommend for or against the use of UV lamps in individuals with CF [6].

Because fat malabsorption is a major postulated mechanism for poor vitamin D absorption, vehicle of vitamin D administration has been investigated. Small studies have suggested that, unlike in the general population, oral supplements can be provided as powder vehicles for vitamin D3 supplementation which may be more efficiently absorbed in cystic fibrosis patients than oil vehicles [70].

Finally, timing, dose and duration of treatment can be affected by seasonality and compliance. To our knowledge, there are no randomized-controlled trials examining the effect of weekly versus daily dosing on subsequent serum levels in patients with cystic fibrosis. The current recommendation is to prescribe once-daily vitamin D3, or its weekly equivalent, tailored to patient compliance. Because the absorption profile of vitamin D in patients with cystic fibrosis may not be similar to the general healthy population, future study is recommended to determine whether once daily or once weekly dosing is superior. Moreover, seasonality may affect dosing needs. A single study looking at seasonal variation in dosing showed that the variations in vitamin D levels were mitigated by doubling the dose in the winter [61].

Clinical practice guidelines have made recommendations for optimal dosing regimens in children and adults [7]. Alternatives to the traditional daily or once weekly dosing described in the guidelines have been only marginally examined for safety and efficacy in this population. For example, whether Stoss therapy – defined as high dose oral vitamin D administration, usually 100,000–600,000 IU/week - is more effective in achieving sufficient vitamin D levels in patients with cystic fibrosis is unknown. A pediatric study in patients with CF showed Stoss therapy to be effective without causing toxicity, with 75% of patients achieving vitamin D sufficiency [71]. Some small retrospective studies suggest that in adult patients, high dose vitamin D supplementation may help achieve sufficient levels [72]. However, caution should be taken with high dose vitamin D therapy, since toxicity can be observed when doses > 50,000 IU/day or when serum levels of 25-hydroxyvitamin D exceed 100–150 ng/ml [3].

The CFF made their most recent set of treatment recommendations (2012) more aggressive after finding that patients were not achieving sufficient 25-hydroxyvitamin levels with the less aggressive past sets of recommendations [7]. Clinicians should check 25-hydroxyvitamin D levels at least yearly at the end of winter to account for seasonal variation. Total 25-hydroxyvitamin D is the preferred serum value to assess, as it accounts for vitamin D produced from the skin and obtained from the diet and has a longer half-life than 1,25-hydroxyvitamin D. The first step in correcting vitamin D insufficiency is assessment and improvement of compliance. Doses are escalated based on serum levels with

**Table 3**

2012 CFF Guidelines for Cholecalciferol (Vitamin D3) Treatment to Goal > 30 ng/ml.

| Age                | Starting dose (IU/day) | First increase (IU/day) | Maximum dose (IU/day) |
|--------------------|------------------------|-------------------------|-----------------------|
| <12 months         | 400–500                | 800–1000                | 2000                  |
| 12 months–10 years | 800–1000               | 1600–3000               | 4000                  |
| >10 years          | 800–2000               | 1600–6000               | 10,000                |

\*If goal serum vitamin D level of > 30 ng/ml is unable to be achieved after 3 months of maximum dose, refer to endocrinology [7].

children starting at lower doses than adults (Table 3) [7].

### Future directions

While there is a large body of literature that describes the multi-systemic effects of vitamin D sufficiency in the cystic fibrosis population, randomized controlled trials that offer recommendations for ideal treatment regimens to achieve serum targets and maximize clinical effects are needed. Treatment regimens may affect different organ systems with greater or lesser potency, and ideal treatment outcomes should be defined in order to design effective trials. With the advent of new highly effective modulator therapy, it is unknown whether vitamin D sufficiency will be easier to achieve, and whether these drugs will contribute to vitamin D-related clinical outcomes. Highly effective modulator therapy may alter current treatment goals in regards to extra-pulmonary organ systems as lifespan increases, and pulmonary morbidity decreases in cystic fibrosis patients.

### Conclusion

Patients with cystic fibrosis commonly experience vitamin D insufficiency and deficiency. Like our case study, patients with cystic fibrosis are notoriously difficult to treat to sufficiency because of a myriad of reasons. Current treatment guidelines aim to treat to serum levels thought to be sufficient to maintain bone health. However, there is a growing body of literature that suggests that vitamin D may be clinically beneficial for pulmonary, immunologic, gastrointestinal, and endocrinologic health, in addition to other systems. Whether there are more ideal treatment regimens or serum 25-hydroxyvitamin D goals for the clinical health of these organ systems is unknown. For patients such as the one presented here, optimizing compliance with pancreatic enzymes and vitamin D supplementation may be important for multiple aspects of her care. While not recommended in current guidelines, techniques for improving vitamin D absorption such as once weekly dosing, using a powder-based vehicle, and using Stoss may be helpful when looking for techniques to help individuals achieve sufficiency. Patients receiving Stoss therapy should be under the care of an endocrinologist. More research is needed to understand whether vitamin D sufficiency has a threshold at which other organ systems are benefitted, or if there is a continuum on which vitamin D sufficiency may affect overall clinical health of CF patients.

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