

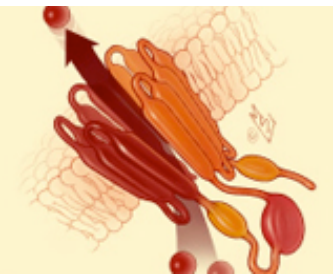


eLITERATURE REVIEW

eCysticFibrosis Review

Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

Supported by Educational Grants from Genentech, Inc., Eurand Pharmaceuticals, Inc., Vertex Pharmaceuticals, Incorporated, Axcan Pharma, Inc. and Gilead Sciences Medical Affairs



HOME CME/CE INFORMATION PROGRAM DIRECTORS NEWSLETTER ARCHIVE EDIT PROFILE RECOMMEND TO A COLLEAGUE



Did you miss our satellite symposium at NACFC or want to refresh your knowledge? Hear five leading clinicians offer their perspective on emerging therapies and how to integrate this information into practice. Listen to the webcast or podcast and earn CE credits for your time.

[LEARN MORE](#)

www.CFseminar09.org

Program Information

- [CME/CE Info](#)
- [Accreditation](#)
- [Credit Designations](#)
- [Intended Audience](#)
- [Learning Objectives](#)
- [Internet CME/CE Policy](#)
- [Faculty Disclosures](#)
- [Disclaimer Statement](#)

Length of Activity

- Physicians
1 hour
- Nurses
1 contact hour
- Dieticians
1 contact hour
- Physical Therapists
1 contact hour

Release Date

June 8, 2010

Expiration Date

June 7, 2012

Podcast Release

July 13, 2010

Next Newsletter Issue

August 10, 2010

June 2010: VOLUME 2, NUMBER 7

Vitamin D and Bone Health

In this Issue...

The aging of the cystic fibrosis (CF) population, associated with advancements in care, has led to the recognition that “adult” illnesses such as osteoporosis and osteopenia are becoming quite common among patients with the disease. The exact cause of CF-related bone disease is unknown, but it is likely multifactorial. One major contributing factor is vitamin D insufficiency, which has an extremely high prevalence among the CF population. Growing evidence suggests that vitamin D deficiency in CF starts very early in childhood and may contribute to subsequent bone health challenges. Understanding the relationship between vitamin D insufficiency and bone disease has been the focus of intense investigation. In this issue, we review recent publications that describe the link between vitamin D insufficiency and bone disease, as well as approaches to treatment of vitamin D insufficiency. We conclude with a discussion of the therapeutic options beyond vitamin D supplementation that are available to treat CF-related bone disease.



LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Define the role of vitamin D in the bone health of patients with cystic fibrosis (CF);
- Describe treatment options for vitamin D insufficiency in the CF population;
- Discuss the use of bisphosphonates for the treatment of bone disease in patients with CF.

TO COMPLETE THE POST-TEST

- Step 1.**
Please read the newsletter.
- Step 2.**
See the Post-test link at the end of the newsletter.
- Step 3.**
Follow the instructions to access the post-test.

IMPORTANT CME/CE INFORMATION

▼ Program Begins Below

ACCREDITATION STATEMENTS

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

Newsletter

- Define the role of vitamin D in the bone health of patients with cystic fibrosis (CF).
- Describe treatment options for vitamin D insufficiency in the CF population.
- Discuss the use of bisphosphonates for the treatment of bone disease in patients with CF.

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. The Institute for Johns Hopkins Nursing and the American Nurses Credentialing Center do not endorse the use of any commercial products discussed or displayed in conjunction with this educational activity.

CREDIT DESIGNATIONS

Physicians

Newsletter: The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses

Newsletter: This 1 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each Newsletter carries a maximum of 1 contact hours or a total of 6 contact hours for the six newsletters in this program.

To obtain contact hours, you must complete this Education Activity and post-test before June 7, 2012.

Dietitians

Newsletter: The Johns Hopkins University has approved this activity for 1.0 contact hours for non-physicians.

Physical Therapists

Newsletter: The Johns Hopkins University has approved this activity for 1.0 contact hours for non-physicians.

Respiratory Therapists

For United States: [Visit this page](#) to confirm that your state will accept the CE Credits gained through this program.

For Canada: [Visit this page](#) to confirm that your province will accept the CE Credits gained through this program.

INTENDED AUDIENCE

This activity has been developed for Pulmonologists, Pediatric Pulmonologists, Gastroenterologists, Pediatricians, Infectious disease specialists, Respiratory therapists, Dietitians, Nutritionists, Nurses, and Physical therapists.

LAUNCH DATE

This program launched on December 8, 2009, and is published monthly; activities expire two years from the date of publication, ending in December 7, 2011.

HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K Modem or better, Windows Media Player 9.0 or later, 128 MB of RAM Monitor settings: High color at 800 x 600 pixels, Sound card and speakers, Adobe Acrobat Reader.

DISCLAIMER STATEMENT

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of Johns Hopkins University name implies review of educational format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings and adverse effects before administering pharmacologic therapy to patients.

SUCCESSFUL COMPLETION

To take the post-test for eCysticFibrosis Review you will need to visit [the Johns Hopkins University School of Medicine's CME website](#) and [the Institute for Johns Hopkins Nursing](#). If you have already registered for other Hopkins CE programs at these sites, simply enter the requested information when prompted. Otherwise, complete the registration form to begin the testing process. A passing grade of 70% or higher on the post-test/evaluation is required to receive CE credit.

STATEMENT OF RESPONSIBILITY

The Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing take responsibility for the content, quality and scientific integrity of this CME/CE activity.

INTERNET CME/CE POLICY

The Office of Continuing Medical Education (CME) at the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing are committed to protect the privacy of its members and customers. The Johns Hopkins University maintains its Internet site as an information resource and service for

Continuing Medical Education at the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing will keep your personal and credit information confidential when you participate in a CE Internet-based program. Your information will never be given to anyone outside the Johns Hopkins

FACULTY DISCLOSURE

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of Johns Hopkins University School of Medicine to require the disclosure of the existence of any relevant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

- **Michael P. Boyle, MD, FCCP** discloses that he has received grant/research support Vertex Pharmaceuticals, Inc.
- **Peter J. Mogayzel, Jr, MD, PhD** discloses that he has no financial relationship with commercial supporters.
- **Meghan Ramsay, MS, CRNP** discloses that she has no financial relationship with commercial supporters.
- **Donna W. Peeler, RN** discloses that she has no financial relationship with commercial supporters.

[Guest Author's Disclosures](#)

IN THIS ISSUE

- [COMMENTARY from our Guest Authors](#)
- [VITAMIN D INSUFFICIENCY AND LOW BONE MINERAL MASS IN PEDIATRIC PATIENTS WITH CF](#)

Program Directors

Michael P. Boyle, MD, FCCP
Associate Professor of Medicine
Director, Adult Cystic Fibrosis Program
The Johns Hopkins University
Baltimore, MD

- [EARLY AGE OF ONSET OF VITAMIN D INSUFFICIENCY IN INFANTS WITH CF](#)
- [INADEQUACY OF CONSENSUS GUIDELINES FOR THE TREATMENT OF VITAMIN D INSUFFICIENCY IN PEDIATRIC PATIENTS WITH CF](#)
- [ADDITIONAL TREATMENT OPTIONS FOR CF PATIENTS WITH VITAMIN D INSUFFICIENCY](#)
- [BISPHOSPHONATES FOR THE TREATMENT OF BONE DISEASE IN ADULT PATIENTS WITH CF](#)

Peter J. Mogayzel, Jr., MD, PhD
 Associate Professor of Pediatrics
 Director, Cystic Fibrosis Center
 The Johns Hopkins University
 Baltimore, MD

Donna W. Peeler, RN, BSN
 Pediatric Clinical Coordinator
 Cystic Fibrosis Center
 The Johns Hopkins University
 Baltimore, MD

Meghan Ramsay, MS, CRNP
 Adult Clinical Coordinator
 Cystic Fibrosis Center
 The Johns Hopkins University
 Baltimore, MD

GUEST AUTHOR OF THE MONTH

Commentary & Reviews:

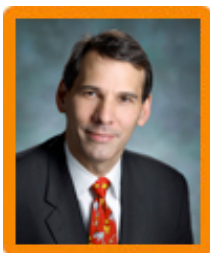


Deanna M. Green, MD
 Pediatric Pulmonary Fellow
 The Johns Hopkins University
 School of Medicine
 Baltimore, Maryland

Guest Faculty Disclosures

Deanna M. Green, MD discloses that she has no financial relationship with commercial supporters.

Peter J. Mogayzel Jr, MD, PhD discloses that he has no financial relationship with commercial supporters.



Peter J. Mogayzel Jr, MD, PhD
 Associate Professor of Pediatrics
 The Johns Hopkins University
 School of Medicine
 Director, Cystic Fibrosis Center
 The Johns Hopkins Hospital
 Baltimore, Maryland

Unlabeled/Unapproved Uses

The authors have indicated that there will be no reference to unlabeled or unapproved uses of drugs or products in the presentation.

[Program Directors' Disclosures](#)

JULY PODCAST



eCysticFibrosis Review is happy to offer our accredited PODCASTS, to be sent to you in July.

The *eCysticFibrosis Review* podcast complements the topic presented in this issue by applying the information to patient scenarios. Our June authors, Deanna Green, MD and Peter Mogayzel, MD and Robert Busker, eCysticFibrosis Review's Managing Editor discuss the topic: Vitamin D and Bone Health.

Participants can now receive 0.75 *AMA PRA Category Credits*™ per podcast after completing an online post-test via the links provided on this page.

To learn more about podcasting and how to access this exciting new feature of *eCysticFibrosis Review*, [please visit this page.](#)

[back to top](#)

As advancements in care continue to evolve, patients with cystic fibrosis (CF) are living well into adulthood. As patients live longer, however, comorbidities such as bone disease are emerging as significant problems among the CF population. CF-related bone disease involves many entities, but the hallmark is decreased bone mineralization (characterized by osteopenia), which leads to pathologic fractures or kyphosis. Multiple factors contribute to bone disease in patients with CF, including malabsorption of vitamin D, poor nutritional status, decreased physical activity, use of glucocorticoids, and delayed puberty. The increasing prevalence of bone disease prompted the CF Foundation to convene a Consensus Conference in 2002 to establish treatment guidelines, which were published in 2005.¹ These guidelines have played a critical role in the care of patients with CF, as they identified bone disease as an entity that could be modified to improve the lives of this patient population.

One prominent, and theoretically easily adjusted, cofactor that contributes to bone disease is vitamin D malabsorption. Vitamin D malabsorption can lead to vitamin D insufficiency, which is defined as a 25-hydroxyvitamin D (25-OHD) level <30 ng/mL (75 nmol/L). The Guidelines Committee recommended that a minimum of 400 IU and 800 IU of vitamin D be provided on a daily basis to infants and to children >1 year of age, respectively. The recommended treatment of vitamin D insufficiency (25-OHD <30 ng/mL) was an 8-week course of 12,000 IU ergocalciferol (vitamin D₂) once weekly for children <5 years of age and 50,000 IU once weekly for patients ≥5 years of age. The guidelines suggested that biweekly regimens may be needed in some patient to attain the goal 25-OHD level. More recently, it has become clear that vitamin D insufficiency is not limited to the CF population.^{2,3} Therefore, more diligence with respect to the recognition and early treatment of vitamin D insufficiency and subsequent bone disease may be necessary. Our goal in this issue is to review current evidence to help clinicians identify patients who are at risk for bone disease, as the guidelines clearly state the following: "Prevention, early recognition, and treatment are the most effective strategies for sustaining bone health to help maintain the quality of life of many individuals with CF."¹ We therefore hope to shed some light on the following issues:

How early in the course of CF treatment do we need to check for bone disease and vitamin D insufficiency?

As the exact onset of CF-related bone disease is not known, determining when to screen patients for bone disease is a difficult question to answer. Only a few studies of bone mineral density (BMD) have been conducted in prepubertal patients with CF. Normative data are now available for healthy children 6 to 16 years of age.⁴ In 2008, Grey and colleagues (reviewed in this issue) used these data to show that Canadian prepubertal CF children had mean *z* scores lower than those in the reference population. The authors further showed, as have many others, that insufficiencies of vitamin D and vitamin K were extremely common, and that deficiencies of vitamin D could be linked to low BMD. Prior recommendations that screening for vitamin D insufficiency be performed only in high-risk CF populations—that is, those with pancreatic insufficiency or those with deficiencies of vitamin A and vitamin E⁵—are no longer adequate. The paper by Neville and Ranganathan demonstrates that vitamin D insufficiency is very common in the newborn period, with no relationship found between vitamin D status and vitamin A levels, vitamin E levels, or pancreatic status. Therefore, screening for vitamin D insufficiency during the newborn period may be the only way in which to adequately identify this problem.

What is the optimal treatment for vitamin D insufficiency?

Shortly after the CF Foundation guidelines were published, Boyle and associates found that the recommended dose of ergocalciferol (50,000 IU once weekly for 8 weeks) did not provide adequate correction of vitamin D insufficiency in adult patients with CF.⁶ Studies of children with CF by Green et al, reviewed in this issue, also demonstrate similar results. In addition, these studies show that other, more aggressive ergocalciferol repletion regimens do not correct low vitamin D levels in a majority of patients. Because oral repletion strategies have proven ineffective in many cases, alternatives to ergocalciferol for the treatment of vitamin D insufficiency have been sought. These alternative treatments include the use of ultraviolet (UV) light and other vitamin D compounds. Khazai and collaborators showed that cholecalciferol may be the optimal

choice for an oral agent to treat vitamin D insufficiency. These investigators also found that UV light may not be an adequate therapy because of noncompliance in the CF population. Ultimately, the majority of studies demonstrate that the current guideline recommendations are inadequate to treat vitamin D insufficiency and that further modifications of these guidelines may be necessary to adequately treat patients with CF.

Are other treatments available that may help improve CF-related bone disease?

Clearly, vitamin D insufficiency is not the only factor that leads to CF-related bone disease. Therefore, the use of other therapies for the treatment of CF-related bone disease has been suggested by several investigators. One therapy recommended in the CF Foundation guidelines is the use of bisphosphonates—a class of agents that inhibit osteoclasts. Early randomized, controlled trials showed that although intravenous (IV) formulations of bisphosphonates were effective in improving BMD, their use was hampered by significant side effects.⁷ Evidence from the study of Canadian adult patient with CF (CFOS trial), reviewed in this issue, shows that an oral bisphosphonate administered once weekly can increase BMD, with limited side effects. This therapy may provide another way in which to combat this escalating disease.

Taken together, the findings discussed in this issue of *eCystic Fibrosis Review* suggest the following: (1) CF-related bone disease and vitamin D insufficiency are very common; (2) increased diligence in screening for both of these conditions may be the only way to adequately prevent future bone disease; (3) current guidelines for the treatment of vitamin D insufficiency are inadequate; and (4) the use of other therapies may be needed to adequately treat bone disease in patients with CF. Additional research is clearly warranted to further explore the level of vitamin D that may prevent bone demineralization and the optimal dose of vitamin D supplementation needed to achieve that goal.

Commentary References

1. Aris RM, Merkel PA, Bachrach LK, et al. [Guide to bone health and disease in cystic fibrosis](#). *J Clin Endocrinol Metab*. 2005;90(3):1888-1896.
2. Black PN, Scragg R. [Relationship between serum 25-hydroxyvitamin D and pulmonary function in the Third National Health and Nutrition Examination Survey](#). *Chest*. 2005;128(6):3792-3798.
3. Wagner CL, Greer FR; American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. [Prevention of rickets and vitamin D deficiency in infants, children, and adolescents](#). *Pediatrics*. 2008;122(5):1142-1152.
4. Kalkwarf HJ, Zemel BS, Gilsanz V, et al. [The Bone Mineral Density in Childhood Study: bone mineral content and density according to age, sex, and race](#). *J Clin Endocrinol Metab*. 2007;92(6):2087-2099.
5. Grey V, Landis L, Pall H, Drury D. [Monitoring of 25-OH vitamin D levels in children with cystic fibrosis](#). *J Pediatr Gastroenterol Nutr*. 2000;30(3):314-319.
6. Boyle MP, Noschese ML, Watts SL, Davis ME, Stenner SE, Lechtzin N. [Failure of high-dose ergocalciferol to correct vitamin D deficiency in adults with cystic fibrosis](#). *Am J Respir Crit Care Med*. 2005;172(2):212-217.
7. Haworth CS, Selby PL, Webb AK, Mawer EB, Adams JE, Freemont TJ. [Severe bone pain after intravenous pamidronate in adult patients with cystic fibrosis](#). *Lancet*. 1998;352(9142):1753-1754.

VITAMIN D INSUFFICIENCY AND LOW BONE MINERAL MASS IN PEDIATRIC PATIENTS WITH CF

Grey V, Atkinson S, Drury D, et al. **Prevalence of low bone mass and deficiencies of vitamins D and K in pediatric patients with cystic fibrosis from 3 Canadian centers**. *Pediatrics*. 2008;122(5):1014-1020.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)



[View journal abstract](#)



[View full article](#)

Although the onset of bone disease in the CF population is believed to begin in childhood, this observation has never been fully established. Additionally, the theory that vitamin D

 **RECOMMEND TO A COLLEAGUE**

 **NEWSLETTER ARCHIVE**

insufficiency may lead to bone disease has also not been fully elucidated in the pediatric population. To address both of these issues, Grey and associates conducted a cross-sectional observational study of 81 pancreatic-insufficient pediatric patients with CF from Canada to assess vitamin D, vitamin K, and bone disease status. The main objective of the study was to determine the extent to which vitamin D and vitamin K status could determine bone mineral status. This study took the novel approach of assessing vitamin K levels directly, rather than using the more common technique of indirect assessment of international normalized ratio (INR) levels. The authors further evaluated multiple cofactors, such as lung function, nutritional status, and physical activity, which could alter the relationship between vitamin status and bone disease. This study was enhanced by the use of multiple markers of bone disease status, including; dual-energy radiograph absorptiometry (DEXA) scans to assess whole-body bone mineral content (WBBMC) and lumbar spine bone mineral density (LSBMD), and multiple blood markers of bone resorption.

Grey and coworkers focused not only on pubescent children, but also on prepubertal children (21 of 81 subjects). A total of 77 (95%) children had vitamin D insufficiency (25-OHD levels <30 ng/mL at the start of the study, despite a vitamin D intake higher than guideline recommendations (subjects were provided with >1000 IU/day). Additionally, 65% of the patients had vitamin K deficiency (defined as a level <0.29 nmol/L), despite only 9 patients having abnormal INR values. Based on DEXA scans, the mean WBBMC and LSBMD *z* scores in this population were less than those in the normative population (*z* score means were <0 across all pubertal groups). In fact, 38% of children had a WBBMC *z* score <-1.0, and 28% of children had an LSBMD *z* score <-1.0 (consistent with low bone mass). Age, height *z* score, and body mass index were all shown to be independent predictors of both WBBMC and LSBMD *z* scores. Tanner stage and 25-OHD level were also found to be predictors of WBBMC *z* score. Although vitamin K levels were not predictive of bone mass, a biomarker of vitamin K deficiency (undercarboxylated osteocalcin [GLU-OC]) was directly proportional to carboxy-terminal propeptide type 1 procollagen (PICP) and osteocalcin (2 biomarkers of bone formation that are suggestive of reduced bone formation when low), and inversely proportional to deoxypyridoline/creatinine ratio (a biomarker of bone resorption that is indicative of increased bone turnover when high).

This study shows that WBBMC and LSBMD are low in about one-third of pediatric patients with CF and that, on average, the bone density of pediatric CF patients is well below that of healthy control populations. Moreover, not only did the authors assess bone disease using DEXA, but they also demonstrated that bone turnover (as measured using osteocalcin, PICP, and urinary deoxypyridinoline/creatinine ratio) was greatly altered in pediatric patients with CF. This study is one of the first to establish that vitamin D levels can predict bone mineral status within the CF population, thus helping to determine whether vitamin D insufficiency is, in fact, a causative factor in bone disease.

[back to top](#)

EARLY AGE OF ONSET OF VITAMIN D INSUFFICIENCY IN INFANTS WITH CF

Neville LA, Ranganathan SC. **Vitamin D in infants with cystic fibrosis diagnosed by newborn screening.** *J Paediatr Child Health.* 2009;45(1-2):36-41.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)



[View journal abstract](#)



[View full article](#)

Vitamin D insufficiency is widespread in the CF population. The exact age of onset of vitamin D insufficiency is unknown, although recent data show that otherwise healthy children in the United States are at significant risk for vitamin D insufficiency early in life.¹ Neville and Ranganathan investigated a newborn CF population to determine whether vitamin deficiencies were present at diagnosis of the disease prior to any



RECOMMEND TO
A COLLEAGUE



NEWSLETTER
ARCHIVE

supplementation. The authors conducted a retrospective, cross-sectional study of infants from Melbourne, Australia, diagnosed with CF between 2001 and 2006. Subjects had vitamins A, E, D, and K levels (assessed by INR) measured within 3 weeks of CF diagnosis. The majority of infants (n=58) were diagnosed with CF secondary to newborn screening, 12 were identified at birth by the presence of meconium ileus, and 3 presented clinically shortly after the newborn period. After initial vitamin levels were obtained, vitamin supplementation was begun.

Median age at CF diagnosis was 1 month; vitamin levels were assessed at a median age of 1.2 months. Vitamin D levels were assessed at diagnosis in 30 of the 73 infants. In these infants, the mean 25-OHD level was 37.1 nmol/L (well below the insufficiency cutoff of 30 ng/mL), with only 3 having a value >30 ng/mL. Of the 73 infants studied, 45 had vitamin A and vitamin E levels obtained, with 60% and 16% of these infants deficient in vitamin A and vitamin E, respectively. All infants had normal INR levels, suggesting that they were vitamin K-sufficient. For those infants in whom vitamin A, vitamin D, and vitamin E levels were assessed, no correlation was found between vitamin D levels and levels of vitamins A or vitamin E. In fact, all 11 infants severely deficient in vitamin D (<10 ng/mL) had normal levels of vitamin E. Additionally, no associations between pancreatic status and vitamin levels were reported. Finally, the birth month of the infant was also not associated with vitamin D status, implying that sunlight in the summer months did not affect vitamin D levels in this population. The authors monitored vitamin D levels in these children and found that after 2 years of vitamin supplementation, no infants whose 25-OHD level was <10 ng/mL were still deficient; however, even after monitoring some patients for up to 60 months, few were found to have vitamin D levels >30 ng/mL.

This study demonstrates that vitamin D insufficiency begins shortly after (if not at) birth within the CF population. Perhaps more importantly, the authors did not find a predictive factor that can be used to determine if an infant is vitamin D-insufficient. In the recent past, certain strategies have been suggested for the assessment of vitamin D insufficiency within the newborn period, including evaluating only those subjects found to be pancreatic-insufficient or first assessing vitamin E levels and, if low, then assessing vitamin D levels.² Based on this study, these strategies would not be effective in identifying subjects with vitamin D insufficiency. Thus, the only effective strategy for identifying vitamin D insufficiency and preventing further deficiency is to test all infants for vitamin status at CF diagnosis, regardless of other clinical factors, and then implement repletion accordingly. Additionally, this study found that with recommended daily supplements of vitamin D 440 IU, few subjects reached the current goal of >30 ng/mL at the first follow-up, implying that higher doses may be necessary for infants to achieve adequate vitamin D levels.

References

1. Wagner CL, Greer FR; American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. [Prevention of rickets and vitamin D deficiency in infants, children, and adolescents](#). *Pediatrics*. 2008;122(5):1142-1152.
2. Grey V, Landis L, Pall H, Drury D. [Monitoring of 25-OH vitamin D levels in children with cystic fibrosis](#). *J Pediatr Gastroenterol Nutr*. 2000;30(3):314-319.

[back to top](#)

INADEQUACY OF CONSENSUS GUIDELINES FOR THE TREATMENT OF VITAMIN D INSUFFICIENCY IN PEDIATRIC PATIENTS WITH CF

Green D, Carson K, Leonard A, et al. **Current treatment recommendations for correcting vitamin D deficiency in pediatric patients with cystic fibrosis are inadequate.** *J Pediatr*. 2008;153(4):554-559.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)



[View journal abstract](#)



[View full article](#)

 RECOMMEND TO A COLLEAGUE

 NEWSLETTER ARCHIVE

Green DM, Leonard AR, Paranjape SM, Rosenstein BJ, Zeitlin PL, Mogayzel PJ Jr. **Transient effectiveness of vitamin D₂ therapy in pediatric cystic fibrosis patients.** *J Cyst Fibros.* 2010;9(2):143-149.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)



[View journal abstract](#)



[View full article](#)

The CF Foundation Consensus Statement encouraged treatment of vitamin D insufficiency, with the hope that this would lead to improvement in BMD. Unfortunately, prior to the publication of these recommendations, few data were available on the appropriate dose of vitamin D needed to achieve adequate levels. The consensus group recommended that ergocalciferol 50,000 IU be used once weekly for 8 weeks to treat vitamin D insufficiency. Green and colleagues initially set out to determine whether this dose was appropriate for the treatment of vitamin D insufficiency in their pediatric population. Using a retrospective analysis, the authors assessed the prevalence of vitamin D insufficiency in their population and discovered multiple cofactors that predisposed an individual to vitamin D insufficiency. They then evaluated the guideline-recommended dose for the treatment of vitamin D insufficiency. Other, more aggressive strategies for the treatment of vitamin D insufficiency had also been in use at Johns Hopkins University.

In the initial year of their study (2003), Green and collaborators found that the prevalence of vitamin D insufficiency was quite high, with 86.5% of their population having vitamin D levels <30 ng/mL. In each subsequent year, the patients studied had a lower prevalence of vitamin D insufficiency; however, even in 2006, almost half of the subjects (46.2%) were still vitamin D-insufficient. Age and the season in which 25-OHD levels were assessed were both shown to be predictive of low vitamin D levels. The success of the various treatment strategies evaluated in the pediatric vitamin D-insufficient patients was compared to also assessed in a cohort of subjects with 25-OHD levels <30 ng/mL who had never been treated with an ergocalciferol regimen (152 patients). Of these 152 untreated patients, 55 (36.4%) had a 25-OHD level >30 ng/mL at follow-up. A total of 21 patients received ergocalciferol 50,000 IU once weekly for 8 weeks, with follow-up levels obtained at the next clinic visit. Only 33% (7 of 21) of the patients had a follow-up level higher than the goal of 30 ng/mL. Ergocalciferol twice weekly for 8 weeks was the next treatment used, which was also shown to be suboptimal, with only 26% (6 of 23) of the subjects responding. The next treatment utilized—ergocalciferol 3 times weekly for 8 weeks—was associated with a greater level of success, with 43% of the population (61 of 141 patients) showing improvement. When each of the different treatments were compared in treated patients vs untreated subjects, none of the treatment regimens was significantly better than the use of no treatment.

As none of the above treatment regimens adequately treated vitamin D insufficiency, in their second paper, Green and colleagues evaluated a new regimen of ergocalciferol 50,000 IU once daily for 4 weeks. The likelihood of successful treatment improved to 54% of those treated (80 of 147 patients). However, this improvement was not sustained, because 13 of the 27 successfully treated individuals had 25-OHD levels <30 ng/mL at the next follow-up and required additional vitamin D supplementation. This implies that once therapy is discontinued, stores of vitamin D quickly become deficient in many cases.

These studies, along with a prior adult study,¹ demonstrate that the recommendations by the CF Foundation Consensus Committee are inadequate for correcting vitamin D insufficiency in the CF population. The recommended regimen of ergocalciferol 50,000 IU once weekly for 8 weeks seems to work in only one-third of patients. Additionally, treatment strategies using very high doses of ergocalciferol were also not successful in maintaining adequate vitamin D levels. This implies that once high-dose therapies are halted, the currently recommended daily supplementation is also inadequate for maintaining 25-OHD levels >30 ng/mL. These studies suggest that increasing daily vitamin D supplementation may be the best way to ensure adequate vitamin D stores. In addition, more frequent monitoring of vitamin D levels may be appropriate if the goal is to have 25-OHD levels >30 ng/mL at all times of the year.

Reference

1. Boyle MP, Noschese ML, Watts SL, Davis ME, Stenner SE, Lechtzin N. [Failure of high-dose ergocalciferol to correct vitamin D deficiency in adults with cystic fibrosis.](#) *Am J Respir Crit Care Med.* 2005;172(2):212-217.

[back to top](#)

ADDITIONAL TREATMENT OPTIONS FOR CF PATIENTS WITH VITAMIN D INSUFFICIENCY

Khazai NB, Judd SE, Jeng L, et al. **Treatment and prevention of vitamin D insufficiency in cystic fibrosis patients; comparative efficacy of ergocalciferol, cholecalciferol, and UV light.** *J Clin Endocrinol Metab.* 2009;94(6):2037-2043.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)



[View journal abstract](#)



[View full article](#)

As mentioned in the Commentary section of this issue, the optimal treatment for vitamin D insufficiency is unclear. The CF Foundation guidelines recommend ergocalciferol in part because it is readily available in prescription form in the United States. Therefore, Khazai and associates sought to compare the efficacy of vitamin D₂ (ergocalciferol), vitamin D₃ (cholecalciferol), and UV light to determine which would be the most beneficial in raising and maintaining the 25-OHD levels above the recommended goal of 30 ng/mL. The authors enrolled 30 individuals with CF, 16 to 70 years of age, in a randomized fashion to receive ergocalciferol 50,000 IU once weekly for 12 weeks, cholecalciferol 50,000 IU once weekly for 12 weeks, or UV light on the subject's back for 3 to 10 minutes 5 times per week. Participants were enrolled only in the winter, in order to minimize sunlight exposure; the randomization was unblinded and not placebo-controlled. Vitamin D levels were assessed using 25-OHD at baseline and within 4 weeks of completion of therapy.

Baseline characteristics were similar in the 3 groups, including initial 25-OHD level. Two-thirds (68%) of the study population were vitamin D-insufficient at the time of enrollment. Treatment with both vitamin D₃ and vitamin D₂ was shown to increase 25-OHD levels significantly, whereas treatment with UV light therapy did not increase 25-OHD levels. The authors examined the mean rate of change and found that those receiving vitamin D₃ had the largest increase. Vitamin D₃ therapy increased 25-OHD levels from a mean of 21.2 ng/mL to 47.1 ng/mL. The response to vitamin D₂ therapy was less dramatic, increasing the mean 25-OHD level from 24.4 ng/mL to 32.7 ng/mL. Parathyroid hormone (PTH) levels were also assessed in this study. After controlling for the baseline value, PTH levels were shown to decrease the most in those treated with the oral vitamin D regimens. Of further note, 45% of the subjects treated with UV therapy were noncompliant with the therapy, using the provided UV light source <80% of the recommended time.

This study is the first of its kind to directly compare the use of ergocalciferol with cholecalciferol and UV light. Based on the findings of the study, it appears that cholecalciferol is at least as effective as ergocalciferol and may, in fact, be a better treatment option for vitamin D insufficiency in patients with CF. Several prior studies have demonstrated that cholecalciferol may remain active slightly longer than ergocalciferol,^{1,2} thereby providing more stable levels of vitamin D for patients. Moreover, it appears that UV light is not a viable option for the treatment of vitamin D insufficiency in persons with CF. Although participants were asked to use the UV light for 10 minutes 5 times weekly, only 55% of the subjects were able to comply with this treatment >80% of the time. As the care of patients with CF is already quite complex, treatment with UV light seems to be inadequate.

References

1. Armas LA, Hollis BW, Heaney RP. [Vitamin D₂ is much less effective than vitamin D₃ in humans.](#) *J Clin Endocrinol Metab.* 2004;89(11):5387-5391.

 RECOMMEND TO A COLLEAGUE

 NEWSLETTER ARCHIVE

2. Trang HM, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R. [Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2](#). *Am J Clin Nutr*. 1998;68(4):854-858.

[back to top](#)

BISPHOSPHONATES FOR THE TREATMENT OF BONE DISEASE IN ADULT PATIENTS WITH CF

Papaioannou A, Kennedy CC, Freitag A, et al. **Alendronate once weekly for the prevention and treatment of bone loss in Canadian adult cystic fibrosis patients (CFOS trial)**. *Chest*. 2008;134(4):794-800.

(For non-subscribers to this journal, an additional fee may apply to obtain full-text articles.)



[View journal abstract](#)



[View full article](#)

Although the recommendations on vitamin D supplementation were an important topic in the consensus statement on bone disease, this was not the only therapy suggested. Another proposed treatment option was the use of bisphosphonates—a class of drugs that exert inhibitory effects on osteoclasts. These medications can reduce bone turnover and increase BMD. Papaioannou and coworkers conducted a double-blind, placebo-controlled, randomized study of alendronate, an oral bisphosphonate, once weekly in patients with CF who had low BMD (T-score of <-1.0 , as measured by DEXA). The authors enrolled 56 adults with CF from 6 centers in Canada. Participants received vitamin D 800 IU and calcium 1000 mg daily, plus either alendronate 70 mg or placebo once weekly, for 12 months. BMD was rechecked by DEXA at completion of therapy.

The 56 individuals enrolled in this study were all young adults (mean age, 29 years) with moderate pulmonary disease (mean forced expiratory volume in 1 second [FEV₁] 57% predicted). Baseline lumbar T-score was -1.65. A multivariable regression was performed to control for various differences among the enrollees, including calcium levels, lung function, age, and baseline BMD. Using this model, treatment with alendronate was associated with a 4% greater increase in LSBMD and a 3% greater increase in hip BMD vs placebo. In fact, the absolute percent change in LSBMD was approximately 5% in the alendronate group, compared with a decrease of -0.08% in LSBMD in the control group. Two new vertebral fractures were reported in the control group and none were observed in the alendronate group. Alendronate seemed to be well tolerated, with no reports of severe bone pain, as has been observed with the administration of IV bisphosphonates.¹ The most common adverse events were pulmonary exacerbations (3 in the alendronate group and 3 in the control group), followed by gastrointestinal complaints (10 with alendronate vs 7 with placebo), which included 1 intestinal obstruction in the alendronate group and 1 in the placebo group.

This study is the first to assess the use of an oral weekly bisphosphonate regimen for the treatment of low BMD in patients with CF. Since CF treatment regimens are already quite complex, a once-weekly regimen that does not involve IV therapy is quite appealing. Based on the results of this study, it appears that alendronate does improve BMD by approximately 4% over 1 year. Clinically relevant improvements in BMD ranged from 2% to 6%, suggesting that this regimen provided worthwhile improvement. This study also demonstrated that since a decline in BMD can occur in just 1 year, frequent DEXA scans may be needed in the CF population to better monitor the onset of bone disease.

Reference

1. Haworth CS, Selby PL, Webb AK, Mawer EB, Adams JE, Freemont TJ. [Severe bone pain after intravenous pamidronate in adult patients with cystic fibrosis](#). *Lancet*. 1998;352(9142):1753-1754.

[back to top](#)

 RECOMMEND TO A COLLEAGUE

 NEWSLETTER ARCHIVE

COMPLETE THE POST-TEST

Step 1.
Click on the appropriate link below. This will take you to the post-test.

Step 2.
If you have participated in a Johns Hopkins on-line course, login. Otherwise, please register.

Step 3.
Complete the post-test and course evaluation.

Step 4.
Print out your certificate.

PHYSICIAN
POST-TEST

NURSE
POST-TEST

DIETICIAN
POST-TEST

PHYSICAL THERAPIST
POST-TEST

* (The post-test for the newsletter is 1 credit hour.)

Respiratory Therapists
[Visit this page](#) to confirm that your state will accept the CE Credits gained through this program or click on the link below to go directly to the post-test.

RESPIRATORY
THERAPIST
POST-TEST

© 2010 JHUSOM, IJHN and *eCysticFibrosis Review*

Presented by [JHUSOM](#) and [IJHN](#) in collaboration with [DKBmed](#).



Illustration © Michael Linkinhoker