JOHNS HOPKINS MEDICINE eLITERATURE REVIEW

eCysticFibrosis Review

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

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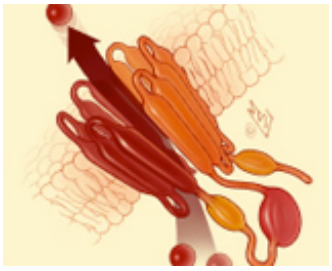

eCysticFibrosis Review VOLUME 4, ISSUE 3

Editor's Note *On June 13 join Johns Hopkins and other international faculty for a live symposium at the 36th annual European Cystic Fibrosis Society conference in Portugal. This will be an interactive case-based presentation supported by incredible 3D animation and 4D effects. For more information about registering, please visit AOTC4D.org. Thanks for your continued participation!*

Strategies to Improve Nutrition Outcomes

In this Issue...

The field of cystic fibrosis nutrition continues to evolve. Current research is exploring not only ways to increase survival, but also to improve the quality of life for those with CF through better health and decreased co-morbid complications. New approaches show that nutrition therapies and resulting status improvements can affect relevant clinical outcomes.

In this issue, we review studies that:

- look at the impact of early nutrition on clinical outcomes
- describe how fecal elastase changes during the first year of life
- investigate genetic modifiers in CF
- explore how diet affects fatty acid status
- evaluate the impact of vitamin D supplementation on inflammation and clinical outcomes

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Discuss current advances in CF nutrition care
- Describe the association between early nutrition status and clinical outcomes
- Summarize strategies to improve nutrition outcomes in individuals with CF

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IMPORTANT CME/CE INFORMATION ▼ Program Begins Below

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Length of Activity
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Release Date
April 30, 2013

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April 29, 2015

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LAUNCH DATE

This program launched on February 28, 2013 and is published monthly; activities expire two years from the date of publication.

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STATEMENT OF NEED

Based on a review of the current literature, including national and regional measures, detailed conversations with expert educators at Johns Hopkins, and a survey of potential program participants, this program will address the following core patient care gaps:

Disease-Modifying Therapies

- Clinicians may be unfamiliar with recently introduced disease-modifying therapies and how they are altering the therapeutic landscape for patients with cystic fibrosis.
- Clinicians may be uncertain how to integrate genotyping into therapeutic decisions and how to communicate with patients and families about the relationship between genotype and therapy

Nutrition

- Many clinicians lack strategies to persuade patients to adhere to CF nutritional requirements, resulting in low body weight and nutritional failure in patients with cystic fibrosis.

- Many clinicians remain uncertain how to optimize pancreatic function in patients with cystic fibrosis.

Treating CF Patients with Inhaled Antibiotics

- Clinicians lack knowledge about the use of existing and emerging inhaled ABX to treat chronic pulmonary infections.

Michael P. Boyle, MD, FCCP discloses that he has served as a consultant for Vertex, Novartis, Genentech, Savara, Pharmaxis, and Gilead Sciences, Inc. He has also received grant/research support from Vertex.

No other planners have indicated that they have any financial interests or relationships with a commercial entity.

Guest Author's Disclosures

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- Clinicians need more information to make informed decisions about the use of inhaled ABX in combination.
- Clinicians lack information about best practices for scheduling ABX therapy to suppress chronic airway infections.
- Common clinician assumptions about treating pulmonary exacerbations lack supporting evidence.
- CF clinicians are not aware of and/or are not actively advocating inhaled ABX patient-adherence strategies.

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Guest Faculty Disclosures

The author has indicated that she has served as a consultant for Abbott Pharmaceuticals.

Unlabeled/Unapproved Uses

The author has indicated that there will be no references to unlabeled or unapproved uses of drugs or products.

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COMMENTARY

Nutrition has become an integral part of care for people with cystic fibrosis (CF). Over the past 30 years, advances have been made in the quest to improve nutritional status, clinical outcomes, and survival in this population.[1-3] The Cystic Fibrosis Foundation (CFF) has developed guidelines and recommendations for many aspects of nutrition therapy.[2-5] While these recommendations are based on currently available information, in this dynamic arena new data is constantly presented. Evaluating new options and approaches for nutrition therapy can provide the practitioner with additional means to improve care and clinical outcomes.

One area of CF care that has evolved over time is the recommendation that all individuals with CF aim to achieve a body mass index (BMI) ≥ 50%.[3] There is a documented association between BMI and pulmonary function, measured as forced expiratory volume 1 second (FEV_1) percent predicted.[6] Others have looked at the impact of short stature, weight at age two, and recovery of birth weight z score as related to later lung function.[7-9] Yen and colleagues evaluated data from the CF Patient Registry (reviewed in this issue). Their study reported an association between the weight for age percentile (WAP) at age four and FEV_1 and survival. They also found that a higher WAP at age four was associated with better linear growth, decreased hospital days, and decreased number of acute exacerbations. This work highlights the critical importance of early and aggressive nutrition therapy.

With the adoption of newborn screening (NBS) as standard practice in the United States, CF care can begin shortly after birth. Since many infants are asymptomatic at diagnosis, the decision about when (or whether) to start pancreatic enzyme replacement therapy (PERT) is not always clear.[4] O'Sullivan's group reports serial fecal elastase values of 61 infants from birth to one year (reviewed in this issue). They found that levels vary throughout the first year of life and that taking only one measurement is not always sufficient. Patients with an initial value < 50 µg/g continued to be pancreatic insufficient (PI) at one year, but some patients with an initial value above 50 µg/g were pancreatic sufficient (PS) by the end of the study. Although this is not a common occurrence, the authors recommend checking fecal elastase at diagnosis and again at one year if the initial value is > 50 µg/g. Genetic testing for mutation analysis may also be helpful, but not all genotypes have a documented PI or PS designation. Clinical judgment should be used in conjunction with test results.

Since the *CFTR* gene was identified in 1989, CF mutation analysis has become common practice in the CF population.[10] Mutation analysis can provide additional clues about disease progression, but it does not tell the whole story. Bradley and colleagues looked at genetic modifiers of nutritional status in cystic fibrosis to try to determine what other genetic factors are involved in nutritional status. In the study reviewed herein, the authors looked at twins and siblings enrolled in the CFF Twin-Sibling study to try to elucidate other genes that are involved in nutritional outcomes and identified regions on chromosomes 1 and 5 that appear to have an effect on nutritional status. While this information will not change clinical practices now, it is possible that in the future we will be able to target specific interventions based on identified genetic modifiers.

Another area of research that is evolving is fatty acid status in CF. Current CFF guidelines provide recommendations for the amount of fat for individuals with CF to consume but do not specify the type because there is not sufficient data to determine an optimal fat source.[3] The fat recommendation is related to weight gain and prevention of essential fatty acid deficiency. It has been documented that people with CF have serum fatty acid (FA) abnormalities.[11] Maqbool's group looked at the relation between dietary fat intake type and serum fatty acid status in children with CF; they found that the kinds of fat that impact serum levels include LA (linoleic acid), DHA (docosahexaoic acid), triene:tetraene (T:T), and arachadonic acid (AA):DHA (reviewed in this issue). They suggest that these serum markers can be improved by increasing alpha linoleic acid (ALA) and LA in the diet. The additions of foods such as flaxseed oil, canned tuna, walnuts, canola, safflower, or sunflower oil may be a noninvasive way to improve fatty acid profiles. The promotion of "heart healthy" fats in CF has not been well studied, but these data suggest these types of diet changes provide a benefit.

Bone disease and vitamin D insufficiency in people with CF have been well documented.[16-18] Vitamin D's role outside of the bones, specifically as related to inflammation, is an area of increasing interest.[19] Grossman and colleagues looked at a novel method for vitamin D repletion during hospitalization for pulmonary exacerbation. In a randomized, controlled pilot study, they gave 250,000 IU of vitamin D_3 to adults admitted for pulmonary exacerbation. The treatment and placebo groups were followed for 12 months posttreatment, and clinically relevant outcomes were evaluated. In the treatment group there was an increase in serum vitamin D, a decrease in the number of hospital days and days on antibiotics, and an improved FEV_1 and survival. In a separate arm of the study (reviewed in this issue) they looked at inflammatory markers in the same groups, finding that in the vitamin D treatment group, tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), both markers of inflammation, were decreased and antimicrobial

peptide LL-37 was increased. These results suggest that vitamin D could potentially decrease inflammation in CF. As vitamin D plays a major role in people with CF, its impact likely extends beyond the bones.

As the world of CF nutrition continues to evolve, the focus is shifting to include more than just weight gain and preventing micronutrient deficiencies. Nutrition can be used as a tool to improve overall health. Nutrition interventions can affect relevant clinical outcomes through early intervention and individualized care.

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EARLY NUTRITION AND HEALTH OUTCOMES

Yen EH, Quinton H, Borowitz D. **Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis.** *J Pediatr.* 2012 Oct 11.

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This prospective, observational study evaluated nutritional status early in life and its impact on the timing and velocity of height growth, lung function, complications of cystic fibrosis (CF) and survival. Using the data from the United States CF Patient Registry, the authors analyzed data from 3142 patients born between 1989 and 1992. Patient data was obtained during clinic visits at accredited CF care centers. Peak weight for age percentile (WAP) at 4 to 5 years was identified for each patient. The authors chose to study WAP instead of body mass index (BMI) because there was concern that BMI would mask nutritional stunting; the age range of 4 to 5 years was used because most people with CF reach their peak WAP by age 4 years. For analysis, the WAP data was stratified into four groups: < 10^{th} percentile, ≥ 10^{th} to < 25^{th} percentile, ≥ 25^{th} to < 50^{th} percentile , and ≥ 50^{th} percentile. The outcomes evaluated were height for age percentile (HAP), pulmonary function (FEV_1 %) predicted, BMI, number of acute pulmonary exacerbations, days hospitalized for pulmonary exacerbations, impaired glucose tolerance, cystic fibrosis related diabetes (CFRD), *Pseudomonas aeruginosa* infection, and survival.

The authors found that patients with a WAP ≥ 50 percentile had a higher HAP at an earlier time ($P < 0.0001$). This trend was also observed with the other cohorts: WAP 25-50 percentile had a height advantage over WAP 10-25. The authors concluded that there is a strong association between WAP at 4 years and height throughout life. The authors also found a correlation between FEV_1 % predicted, as a measure of pulmonary function, and WAP at age 4 ($P < 0.001$). The FEV_1 % predicted for the WAP > 10% group was considerably lower than all other groups and never reached 80%. For the other groups, FEV_1 % predicted increased with each higher WAP group. There was no difference found between the groups with respect to the rate of pulmonary decline. The authors noted a strong association between WAP at age 4 and linear growth ($P < 0.001$). Height category at age 4 was noted to be associated with survival. Survival at 18 years was better for both higher WAP and HAP groups ($P < 0.001$). The authors also found an association between higher WAP at age 4 and a decreased number of acute exacerbations ($P < 0.05$) and hospital days ($P < 0.05$). No difference was found in *Pseudomonas aeruginosa* infection among the groups.

The authors concluded that their data confirmed short-term studies looking at nutrition status in young children and lung function or survival. FEV_1 % predicted during childhood and adolescence is lower in patients with a WAP < 10 % at age 4 years. Their study also shows that WAP at age 4 years has a significant association with clinically relevant endpoints such as acute exacerbations, hospital days, and survival at age 18 years. With nutritional intervention, patients with CF can approach the growth velocity of healthy controls. Although CFTR dysfunction may influence growth, the effects may be modified with improved nutritional status.

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FECAL ELASTASE DURING THE FIRST YEAR OF LIFE

O'Sullivan BP, Baker D, Leung KG, Reed G, Baker SS, Borowitz D. **Evolution of Pancreatic Function during the First Year in Infants with Cystic Fibrosis.**
J Pediatr. 2013 Apr;162(4):808-812

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In this study, O'Sullivan and colleagues looked at how pancreatic function changes during the first year of life using serial measurements of fecal elastase — a topic of great interest because some infants with cystic fibrosis diagnosed by newborn screening may be pancreatic

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sufficient (PS) at diagnosis and become pancreatic insufficient (PI) as they grow older. The authors report that the majority of past studies using fecal elastase were cross-sectional with single samples. Their goal was to determine how fecal elastase values change as the babies age by providing a longitudinal evaluation of pancreatic function during the first year of life.

The subjects in this study were part of a larger trial investigating the effect of docosahexanoic acid (DHA) supplementation in infant formula. The subjects were all formula fed and entered into the study by 54 days of life, with data collected for 61 infants. The patients had varied mutations: 28 (46%) homozygous F508del, 10 compound heterozygotes that had genotypes associated with PI, and 5 others with F508del and an unidentified mutation. The infants were grouped based on their initial fecal elastase value (< 50 µg/g, 50-100 µg/g, 100-200 µg/g, and > 200 µg/g). Twenty-nine infants had an initial fecal elastase < 50 µg/g. Although three had a fecal elastase > 200µg/g at some time during the first year of life, all had a value < 200 µg/g at 1 year of age. Seven infants had an initial fecal elastase between 50-100 µg/g: 6 of these had a value >100 µg/g at 1 year of age, and one had a fecal elastase consistent with PS (> 200µg/g) at the end of the study (the mutation for this baby is known to be associated with PS in approximately 40% of cases). Greater variability was seen in the initial fecal elastase in the 100-200 µg/g group, where 48 infants had initial values consistent with PI:4 of these ended up with PS values (> 200 µg/g), while 13 others had at least one value > 200 µg/g during the study period.

The authors note significant variability in the fecal elastase values during the first 12 months of life, with many fecal elastase values not consistent with either their initial or final result. They suggest that infants with low values (< 50 µg/g) are unlikely to become PS, and while an initial level > 50 µg/g but < 200 µg/g may change over time, the majority of infants with an initial fecal elastase <200µg/g will remain PI. Frequent retesting may be confusing and is not recommended unless the initial value is > 50 µg/g, and for those infants, retesting at 1 year of age is recommended. The authors report that genotype is an important determinant of pancreatic function, however, they believe that phenotype (fecal elastase test) is a better indicator: for example, 2 infants with F508del ended the study period above 200 µg/g, which is consistent with PS.

The investigators recommend that management decisions about pancreatic enzyme replacement therapy (PERT) should not be based on a single fecal elastase measurement or genotype determination but should include multiple data points.

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GENETIC MODIFIERS AND NUTRITION

Bradley GM, Blackman SM, Watson CP, Doshi VK, Cutting GR. **Genetic modifiers of nutritional status in cystic fibrosis.** *Am J Clin Nutr.* 2012 Dec;96(6):1299-308.

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Although improved nutrition early in life is associated with better pulmonary outcomes, nutritional status is poorly correlated with the *CFTR* genotype, suggesting the influence of additional variables such as environment or other genetic factors. Identifying modifier genes is important because they could provide an etiology and potential target for therapeutic intervention for poor nutrition after other therapies have been optimized. In this study, Bradley and colleagues investigated the potential effect of genetic modifiers on nutritional outcomes in CF.

The authors theorized that BMI phenotype was heritable and that modifier genes contribute to the variability in the nutritional status of children. They used data from the CF Twin-Sibling Study to investigate the impact of genetic and non-genetic factors on nutritional outcomes, with BMI used as the indicator of nutritional status. The analysis of twins and siblings allowed the authors to segregate environmental and genetic effects.

Longitudinal height and weight data was collected from 2000-2010. The BMI phenotype ($BMI_{Z\ 5\text{-}10}$) was derived using BMI data from 1124 children ages 5 to10 years, determined by the average peak BMI per quarter. Covariates that had previously been shown to confound

nutritional status were evaluated to assess their contributions to $BMI_{Z\ 5\text{-}10}$ variability. These included gender, birth cohort, age at CF diagnosis, diagnosis by newborn screening (NBS), homozygosity for F508del *CFTR* mutation, severe exocrine pancreatic insufficiency (PI), history of meconium ileus (MI), presence of a gastrostomy tube, pulmonary function (FEV_1), and socioeconomic status. Pancreatic sufficiency (PS) was defined as having at least one *CFTR* mutation associated with pancreatic sufficiency.

Linkage analysis suggested two genes located on chromosomes 1 and 5 have influence on the BMI phenotype. When the $BMI_{Z\ 5\text{-}10}$ was adjusted for lung function (FEV_1), the linkage evidence to the locus on chromosome 1 decreased but the adjustment did not affect the strength of the locus on chromosome 5. The authors suggest that modifier genes on chromosome 1 could affect both nutrition and lung function and those on chromosome 5 only affect nutrition. $BMI_{Z\ 5\text{-}10}$ was positively correlated to later birth cohorts ($P \leq 0.001$) and lung function ($P \leq 0.001$), and negatively correlated with PI ($P = 0.08$) and history of MI ($P = 0.01$). The phenotype was also negatively correlated with female gender, but the value was not significant. The authors conclude that genes other than *CFTR* influence variation in BMI, and that the identification of modifier genes could provide targets for future nutritional interventions.

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IMPACT OF DIET ON FATTY ACID STATUS

Maqbool A, Schall JI, Gallagher PR, Zemel BS, Strandvik B, Stallings VA. **Relation between dietary fat intake type and serum fatty acid status in children with cystic fibrosis.** *J Pediatr Gastroenterol Nutr*. 2012 Nov;55(5):605-11.

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In this study, Maqbool and colleagues discuss essential fatty acid deficiency (EFAD) and fatty acid (FA) abnormalities in CF. The most frequently described abnormalities are decreased linoleic acid (LA) and docosohexanoic acid (DHA) concentrations, and abnormal triene:tetraene (T:T) and arachidonic acid (AA):DHA ratios. The current CF Foundation guidelines provide macronutrient recommendations for people with CF, but not the type of fats they should consume. The aim of the study is to determine whether type of dietary fat predicted serum LA, DHA, T:T, and AA:DHA in preadolescent children with CF and pancreatic insufficiency (PI).

The authors used cross-sectional nutritional status and progression of pulmonary disease in children with CF and PI ages 7-10 years. Exclusion criteria included $FEV_1 < 40\%$ predicted, significant liver disease, insulin dependent diabetes mellitus, *Burkholderia cepacia* sputum colonization, or other medical conditions known to affect growth. Data from healthy controls of similar age, gender, and ethnic background from a study of bone health were used as a comparison. Intake was assessed using a seven-day home based, weighed food record. Intake of total fat, saturated fatty acid (SFA), monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid (PUFA), total omega 6 PUFA, total omega 3 PUFA, LA, DHA, alpha linoleic acid (ALA), and AA were also reported. Fasting serum phospholipid FA was obtained for all CF subjects. Nonfasting serum phospholipid FA assessment was used for the healthy controls.

The authors evaluated 65 subjects with CF and PI and 22 healthy controls. There were no significant differences between the subjects with CF and healthy controls with respect to age, sex and growth status. CF subjects had higher energy P = 0.0005) and LA intakes ($P = 0.005$) and had lower serum LA, DHA values and higher T:T and AA:DHA ratios when compared to the healthy controls ($P < 0.0005$). The type of dietary fat intake predicted serum FA outcomes in subjects with CF and healthy controls.

LA concentration has been shown to be associated with growth and lung function in pediatric patients with CF; it is considered to be a more relevant EFA status marker than T:T ratio. The authors theorize that increasing specific fats, such as ALA, may allow for the preservation of LA. For example, dietary ALA can be increased by adding flaxseed, walnut, or rapeseed

(canola) oil. Increased dietary LA, in the form of corn, safflower, and sunflower oils, may compensate for increased LA turnover. The investigators concluded that the type of dietary fat influences serum FAs associated with clinically relevant outcomes and inflammation. Further study in this area is needed.

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HIGH DOSE VITAMIN D THERAPY DURING EXACERBATIONS

Grossmann RE, Zughaier SM, Kumari M, et al. **Pilot study of vitamin D supplementation in adults with cystic fibrosis pulmonary exacerbation: a randomized, controlled trial.** *Dermatoendocrinol.* 2012 Apr 1;4(2):191-7.

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Grossmann RE, Zughaier SM, Liu S, Lyles RH, Tangpricha V. **Impact of vitamin D supplementation on markers of inflammation in adults with cystic fibrosis hospitalized for a pulmonary exacerbation.** *Eur J Clin Nutr.* 2012 Sep;66(9):1072-4.

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Vitamin D insufficiency may be detrimental in the CF population and has been linked to many prevalent conditions such as low bone mineral density, diabetes, decreased lung function, respiratory infections, and dysregulation of the immune response, as well as to increased systemic inflammation. Working under the hypothesis that improving vitamin D status would improve clinical outcomes in CF, this randomized, placebo-controlled pilot study investigated the feasibility and impact of high-dose oral vitamin D_3 supplementation with 48 hours of admission for a pulmonary exacerbation. Grossman and colleagues administered high dose oral vitamin D_3 (250,000 IU) at the time of hospital admission to rapidly increase vitamin D status. Findings reported included serum 25 hydroxy vitamin D (25(OH)D), parathyroid hormone (PTH), and calcium levels. Clinical outcomes evaluated were survival, hospitalizations, IV antibiotic therapy, and lung function up to 12 months after randomization.

Fifteen subjects with similar baseline characteristics were enrolled in each group (Vitamin D_3 supplementation and placebo). Serum 25(OH)D levels were measured at baseline, one week, and 12 weeks. Mean serum 25(OH)D levels were similar at baseline. Sixty percent of subjects in the treatment group and 40% of the placebo group were sufficient in vitamin D (≥ 30 ng/mL). At one week, mean serum 25(OH)D increased by 27.5 ± 3.8 ng/mL ($P < 0.001$) in the treatment group and decreased by 0.2 ±1.4 ng/mL in the placebo group ($P = 0.64$). There was no evidence of vitamin D toxicity in the treatment group. The highest individual 25(OH)D value was 83 ng/mL. Serum calcium levels were similar between the groups and did not change with treatment. The treatment group had a decrease in the number of hospital days ($P = 0.04$) and days on IV antibiotic therapy ($P = 0.07$) when compared to the placebo group. There was also a trend toward improved lung function, although it was not statistically significant. Statistical analysis suggested a higher risk for death in the placebo group ($P = 0.03$). There was no significant difference in the change in BMI between the two groups.

In the second study, the authors present additional investigating markers of inflammation after administration of 250,000 IU of vitamin D_3, under the hypothesis that increasing vitamin D status may improve antimicrobial peptide concentrations and markers of inflammation. Findings reported include serum interleukin-1β(IL-1β), IL-10, IL-18-binding protein (IL-18-BP),IL-6, IL-8, TNF-α, and plasma antimicrobial peptide LL-37.

The authors report that at one week and 12 weeks, mean serum TNF-α concentrations were significantly lower in the vitamin D treatment group. Compared to baseline, TNF-α decreased by 3.54 ± 8.3 and 27.62 ± 8.4 pg/ml at 1 and 12 weeks, respectively ($P = 0.60$, 0.00002). There was not a significant change in the placebo group. Compared to baseline, mean plasma IL-6 concentrations decreased significantly at one ($P = 0.004$) and 12 weeks ($P = 0.4$); there was not a significant change at 12 weeks. IL-8 increased in both groups but the change did

not differ between the groups and was not significant. Other measures were evaluated but did not show significant differences between groups.

Overall, the authors report that the novel bolus dosing strategy is feasible, did not cause toxicity, was well-tolerated, and is an attractive delivery method to help with adherence. The supplementation may also have improved clinical outcomes by increasing the number of hospital and antibiotic therapy-free days in the six months after the intervention. They also note a trend toward increased recovery of lung function. The investigators theorize that vitamin D sufficiency may increase the production of antimicrobial peptides which may in turn decrease the need for antibiotic therapy, and that vitamin D as a modulator of inflammation may decrease inflammatory damage to the lung tissue. More study is needed in this area.

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