improvement, and other objective outcomes or for further endophenotypic stratifications of for personalized therapeutics. For example, the new BDR framework may prove to be a useful tool in defining asthma–COPD overlap and for other "fuzzy" phenotypes of obstructive lung disease and, possibly, to better define disease subgroups that would benefit more from specific BD agents.

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: The authors thank Kevin McCarthy, Jose Ramos, and James K. Stoller, MD (Cleveland Clinic), for pulmonary function testing data sharing and James K. Stoller, MD (Cleveland Clinic) for critical review of the manuscript.

Octavian C. Ioachimescu, M.D., Ph.D.*
Emory University
Atlanta, Georgia

and

Veterans Affairs Sleep Medicine Center
Decatur, Georgia

ORCID ID: 0000-0001-9047-6894 (O.C.I.).

*Corresponding author (e-mail: oioac@yahoo.com).

References

1 Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, *et al*. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948–968.
2 Hansen JE, Casaburi R, Goldberg AS. A statistical approach for assessment of bronchodilator responsiveness in pulmonary function testing. *Chest* 1993;104:1119–1126.
3 Hansen JE, Porszasz J. Rebuttal from Drs Hansen and Porszasz. *Chest* 2014;146:542–544.
4 Hansen JE, Sun XG, Adame D, Wasserman K. Argument for changing criteria for bronchodilator responsiveness. *Respir Med* 2008;102: 1777–1783.
5 Pellegrino R, Brusasco V. Rebuttal from Drs Pellegrino and Brusasco. *Chest* 2014;146:541–542.
6 Calverley PM, Burge PS, Spencer S, Anderson JA, Jones PW. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. *Thorax* 2003;58:659–664.
7 Hay JG, Stone P, Carter J, Church S, Eyre-Brook A, Pearson MG, *et al*. Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease. *Eur Respir J* 1992;5:659–664.
8 Hansen JE, Dilektasli AG, Porszasz J, Stringer WW, Pak Y, Rossiter HB, *et al*. A new bronchodilator response grading strategy identifies distinct patient populations. *Ann Am Thorac Soc* 2019;16:1504–1517.
9 Standardization of spirometry, 1994 update: American Thoracic Society. *Am J Respir Crit Care Med* 1995;152:1107–1136.
10 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, *et al*.; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
11 American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991;144:1202–1218.
12 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, *et al*.; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–1343.
13 Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, *et al*. Genetic epidemiology of COPD (COPDGene) study design. *COPD* 2010;7:32–43.
14 Freedman BJ, Meisner P, Hill GB. A comparison of the actions of different bronchodilators in asthma. *Thorax* 1968;23:590–597.
15 Criteria for the assessment of reversibility in airways obstruction: report of the committee on emphysema American College of Chest Physicians. *Chest* 1974;65:552–553.
16 Reis AL. Response to bronchodilators. In: Clausen JL, Abramon JF, editors. Pulmonary function testing guidelines and controversies: equipment, methods, and normal values, New York: Academic Press; 1982. pp. 215–221.
17 Eliasson O, Degraff AC Jr. The use of criteria for reversibility and obstruction to define patient groups for bronchodilator trials. Influence of clinical diagnosis, spirometric, and anthropometric variables. *Am Rev Respir Dis* 1985;132: 858–864.
18 Tan WC, Vollmer WM, Lamprecht B, Mannino DM, Jithoo A, Nizankowska-Mogilnicka E, *et al*.; BOLD Collaborative Research Group. Worldwide patterns of bronchodilator responsiveness: results from the Burden of Obstructive Lung Disease study. *Thorax* 2012;67:718–726.
19 Donohue JF. Minimal clinically important differences in COPD lung function. *COPD* 2005;2:111–124.

Vitamin D Deficiency Is Associated with Increased Nontuberculous Mycobacteria Risk in Cystic Fibrosis

To the Editor:

Individuals with cystic fibrosis (CF) are at markedly increased risk of pulmonary nontuberculous mycobacteria (NTM) infection (1–3), which is associated with accelerated lung function decline. Although structural lung disease likely contributes to elevated NTM risk in this population, identification of modifiable risk factors may help to reduce these morbid infections in CF. Vitamin D is important for host control of *Mycobacterium tuberculosis* (4, 5), but to date, few studies have explored the relationship between vitamin D deficiency (VDD) and NTM infection (6). Because of pancreatic exocrine insufficiency, individuals with CF are at high risk for VDD (7). In this analysis, we investigate our hypothesis that VDD is a risk factor for incident NTM respiratory isolation in CF.

Supported by grants from the National Heart, Lung, and Blood Institute/ National Institutes of Health (T32 HL007534–36 and F32HL149178–01) (W.J.R.), Cystic Fibrosis Foundation Student Traineeship Award SUN19HO (Y.S.), K08 HL139994 and Burroughs Wellcome Fund Career Award for Medical Scientists (K.A.C).

Author Contributions: Study conception and initial design: M.T.J. and K.A.C. Methodological input: K.J.P. and N.L. Data acquisition: W.J.R., Y.S., M.N.S., and J.A.N. Data analysis: Y.S. and K.J.P. First draft of the manuscript: W.J.R., Y.S., and K.J.P. Critical revision of the manuscript: A.S., N.L., M.T.J., and K.A.C. Approval of the final version of the manuscript: all authors.

Methods

We conducted a retrospective cohort study of adults (≥18 yr old) with CF cared for at the Johns Hopkins CF Center between January 1, 2007, and December 31, 2018 (institutional review board approval #IRB00153445). Clinical and demographic data were extracted from the CF Foundation Patient Registry (8) and chart review. Individuals with at least one serum 25-OH vitamin D value

during the study period and a mycobacterial culture performed within the subsequent 2 years were eligible for inclusion; individuals could contribute multiple measurements. A 2-year follow-up period from vitamin D concentration measurement was used to account for the indolent nature of NTM infection. Exclusion criteria included history of NTM and/or lung transplantation. The primary outcome of interest was incident respiratory isolation of a potentially pathogenic NTM from sputum or bronchoalveolar lavage. VDD was the primary exposure of interest and was defined as a vitamin D concentration of <20 ng/ml (9).

Statistical analysis. Baseline characteristics were compared between individuals by NTM acquisition status during follow-up. The primary unit of analysis was individual's vitamin D test; as such, an individual could contribute more than one vitamin D measurement to analyses, and multiple vitamin D measurements could have the same mycobacterial culture outcome, if the culture fell within the 2 year follow-up period for each measurement. This methodology was chosen to use all collected data and to allow for more precise estimation of effects while still including individual-level characteristics in a multivariable regression model. Multivariable Cox proportional hazard regression models with robust SEs to account for multiple observations within individuals were used to evaluate the association between VDD and time to incident NTM acquisition. Time at risk was defined as the time from vitamin D test to either NTM acquisition (for those who acquired NTM during follow-up) or the earliest occurrence of either death, lung transplant, administrative censoring, or 2 years (for those who did not acquire NTM). Models included adjustment for *a priori*–identified individual-level factors including age at vitamin D testing, sex, highest body mass index and forced expiratory volume in 1 second (FEV_1) percentage predicted in year before vitamin D testing, pancreatic insufficiency (defined as pancreatic enzyme use) in previous year, and macrolide use in previous year. In a secondary analysis, vitamin D concentration was analyzed as a continuous variable. Results of regression models are presented as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Analyses were performed using STATA version 15.1 (StataCorp).

Results

Study population. We identified 254 individuals who met the inclusion criteria (Figure 1). During the 12-year study period, 50 individuals (19.7%) had a positive NTM culture, with *Mycobacterium avium* as the most commonly identified NTM species (58%). Individuals who acquired NTM had significantly higher FEV_1 and lower rates of macrolide use and *Pseudomonas aeruginosa* (PsA) infection at the time of study entry, but baseline vitamin D concentrations did not differ significantly (Table 1).

Vitamin D concentrations. Individuals remaining NTM negative throughout the study contributed a greater number of vitamin D values (mean ± SD, 5.4 ± 4.1) in comparison with those who became NTM positive (3.5 ± 2.7). The analytic sample was comprised of 1,282 vitamin D measurements among 254

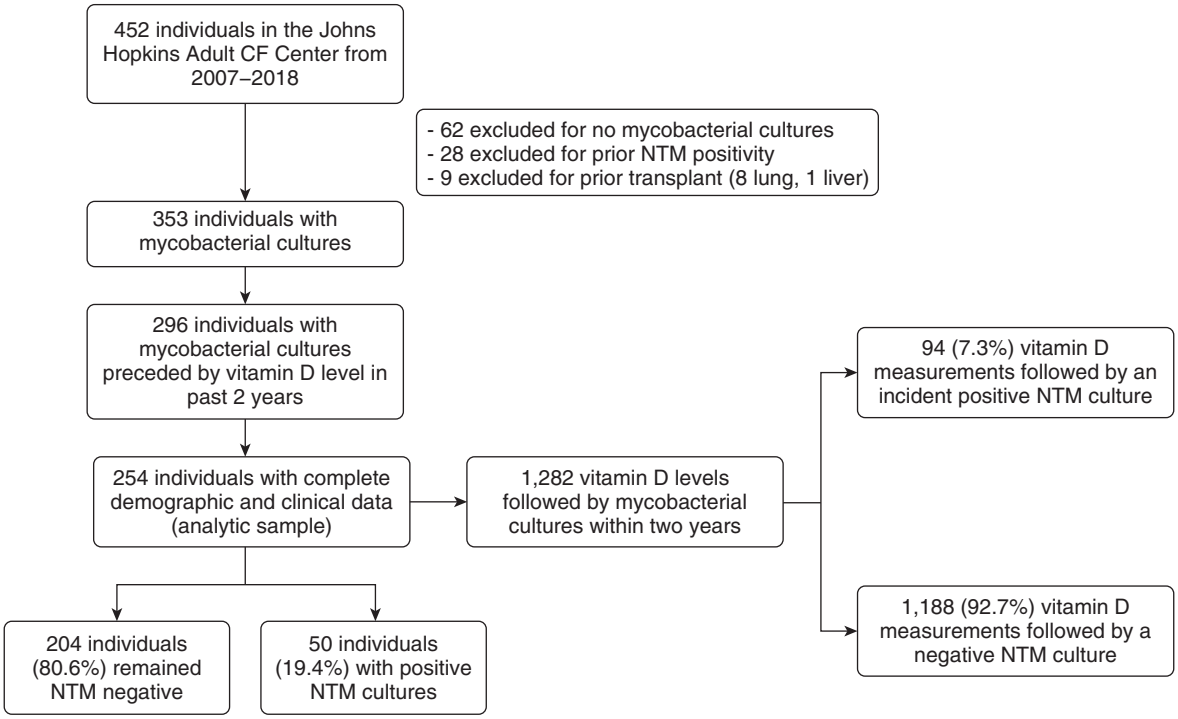

Figure 1. Flowchart of subjects and their vitamin D concentrations. We identified 254 individuals with mycobacterial cultures preceded by vitamin D concentrations in the prior 2 years. Our primary analysis used the vitamin D concentrations as the unit of analysis. From the 254 individuals in our cohort, 1,282 vitamin D concentrations were included in the analysis. Individuals could contribute multiple vitamin D observations, but they could not contribute any vitamin D measurements after an initial NTM positive culture. CF = cystic fibrosis; NTM = nontuberculous mycobacteria.

Table 1. Baseline demographic and clinical characteristics of subjects upon study entry by NTM acquisition status

Subject characteristics	Overall (*n* = 254)	Acquired NTM Infection During Follow-Up (*n* = 50)	Remained NTM Negative (*n* = 204)
Age, mean (SD), yr	30.1 (11.1)	29.0 (9.1)	30.5 (11.5)
Sex, F, *n* (%)	132 (52.0)	22 (44.0)	110 (53.9)
BMI, mean (SD)	23.4 (4.3)	24.3 (3.9)	23.1 (4.4)
Baseline vitamin D values, mean (SD)	26.6 (12.0)	23.9 (11.6)	27.2 (11.8)
FEV_1% predicted, mean (SD)	69.7 (22.3)	78.8 (18.0)	67.5 (22.7)*
CFTR genotype, *n* (%)			
F508del homozygous	118 (46.5)	23 (46.0)	95 (47.0)
F508del heterozygous	109 (41.7)	23 (46.0)	86 (42.2)
Other	23 (9.1)	4 (8.0)	19 (9.3)
Unknown†	4 (1.6)	0 (0.0)	4 (2.0)
CFRD, *n* (%)	45 (17.8)	6 (12.2)	39 (19.0)
Pancreatic insufficiency, *n* (%)	218 (85.8)	45 (90.0)	173 (84.8)
Chronic macrolide use, *n* (%)	207 (76.9)	39 (78.0)	168 (82.4)
Pseudomonas aeruginosa, *n* (%)	193 (76.9)	32 (64.0)	161 (80.1)*
Staphylococcus aureus, *n* (%)	158 (63.7)	35 (70.0)	123 (61.2)
Aspergillus (any species), *n* (%)	73 (29.1)	18 (36.0)	55 (27.4)
NTM species, *n* (%)			
Mycobacterium avium complex		29 (58.0)	—
Mycobacterium abscessus/chelonae		18 (36.0)	—
Other‡		3 (6.0)	—
NTM treatment initiated, *n* (%)		23 (46.0)	—

Definition of abbreviations: BMI = body mass index; CFRD = cystic fibrosis related diabetes; CFTR = cystic fibrosis transmembrane conductance regulator; FEV_1 = forced expiratory volume in 1 s; NTM = nontuberculous mycobacteria; SD = standard deviation.
*Statistically significant with a $P < 0.05$ using Student's *t* tests with unequal variances and χ^2 or Fisher exact tests for continuous and categorical variables, respectively.
†Unknown includes individuals who do not have at least one allele classified. Other includes those with two known alleles, neither of which are F508del.
‡Other NTM species include *Mycobacterium fortuitum* (2) and *Mycobacterium lentiflavum* (1).

individuals (median = 4 measurements/person; range, 1–25 measurements). The average serum vitamin D value was 28.8 ng/ml (SD = 13.7), and 23.0% ($n = 295$) of vitamin D values were categorized as vitamin D deficient (<20 ng/ml). A positive NTM respiratory culture within 2 years of vitamin D measurement was observed after only 94 (7.3%) vitamin D measurements, whereas the remaining 1,188 (92.7%) vitamin D measurements were followed by negative mycobacterial cultures. VDD was more common (35.1% vs. 22.1%; $P < 0.01$) and mean vitamin D values were lower (25.7 ng/ml [SD = 12.28] vs. 29.1 ng/ml [SD = 13.74]; $P = 0.03$) among vitamin D measurements before positive NTM cultures compared with those before negative NTM cultures. Persistent VDD (defined as two or more consecutive vitamin measurements that were vitamin D deficient) was more frequently observed in individuals who became NTM positive (28.0%) than those who remained NTM negative (15.7%).

Primary and secondary analysis. After adjustment for individual-level characteristics, VDD was associated with a significantly higher risk of NTM acquisition (HR, 1.74; 95% CI, 1.12–2.71). Lowering the threshold of VDD from 20 ng/ml to 12 ng/ml resulted in a similar estimate for the association between VDD and NTM infection (HR, 2.05; 95% CI, 1.07–3.91). When vitamin D concentration was evaluated as a continuous variable, it was not associated with increased risk of incident NTM isolation (HR, 0.98; 95% CI, 0.96–1.00).

Discussion

We found that VDD was associated with a higher risk of incident NTM respiratory isolation in adults with CF. Further supporting this association are findings of significantly higher rates of VDD and significantly lower average serum vitamin D concentrations before NTM isolation. Interestingly, when vitamin D was analyzed as a continuous variable, NTM isolation was not significantly associated with lower vitamin D concentrations, suggesting that a threshold may exist below which NTM susceptibility increases. The association between VDD and NTM infection has a biologically plausible explanation based on prior *in vitro* studies demonstrating the role of vitamin D in the immune response to other mycobacteria (5). A recent single-center retrospective study reported that adults with non-CF bronchiectasis with NTM lung disease had a higher prevalence of severe VDD compared with control subjects without NTM (6), although that study evaluated vitamin D concentrations after NTM isolation and is also limited because of its retrospective nature. To our knowledge, this is the first study that has implicated VDD as a potential risk factor in NTM acquisition in CF.

There are limitations to our study. First, although clinical guidelines recommend annual vitamin D measurement (10) and NTM respiratory cultures (11), routine ascertainment in our cohort was highly variable. Our study included only individual's vitamin D measurements with a corresponding NTM culture within 2 years which may have introduced selection bias. At the time of first clinical encounter (separate from first vitamin D measurement), individuals from our institution who were included in this study were older, had lower FEV_1% predicted and higher rates of PsA and macrolide use when compared with those

not included in the study (data not shown). In addition, the exposure–outcome effect estimates may be further impacted because of unmeasured confounding; however, covariates in the final model reflect those that have been previously described to be associated with NTM acquisition. Finally, our study only evaluated incident NTM isolation in CF rather than NTM lung disease (as this was a rare event); however, NTM isolation alone is an important clinical endpoint in CF.

The potential increased risk of NTM conferred by VDD may have important clinical consequence for the management of individuals with CF. More frequent monitoring of vitamin D concentrations and targeted attempts at aggressive repletion—especially in those who are significantly deficient—may warrant investigation as to whether they would reduce the risk of NTM infection. Further prospective studies with larger populations are warranted to better define the relationship between VDD and the risk of NTM infection and disease in CF.

Author disclosures are available with the text of this letter at www.atsjournals.org.

William J. Richter, M.D.*
Yuqing Sun, Ph.D.*
Kevin J. Psoter, Ph.D.
Matthew N. Santos, B.A.
Jan A. Nguyen, M.S.
Aniket Sidhaye, M.D.
Noah Lechtzin, M.D.
Mark T. Jennings, M.D., MHS‡
Keira A. Cohen, M.D.‡§
Johns Hopkins University School of Medicine
Baltimore, Maryland

ORCID ID: 0000-0002-9844-4819 (W.J.R.).

*These authors contributed equally to this work.
‡These authors contributed equally to this work.
§Corresponding author (e-mail: kcohen8@jhmi.edu).

References

1 Adjemian J, Olivier KN, Prevots DR. Nontuberculous mycobacteria among patients with cystic fibrosis in the United States: screening practices and environmental risk. *Am J Respir Crit Care Med* 2014; 190:581–586.
2 Viviani L, Harrison MJ, Zolin A, Haworth CS, Floto RA. Epidemiology of nontuberculous mycobacteria (NTM) amongst individuals with cystic fibrosis (CF). *J Cyst Fibros* 2016;15:619–623.
3 Martiniano SL, Sontag MK, Daley CL, Nick JA, Sagel SD. Clinical significance of a first positive nontuberculous mycobacteria culture in cystic fibrosis. *Ann Am Thorac Soc* 2014;11:36–44.
4 Wilkinson RJ, Llewelyn M, Toossi Z, Patel P, Pasvol G, Lalvani A, *et al*. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. *Lancet* 2000;355:618–621.
5 Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, *et al*. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006;311:1770–1773.
6 Jeon K, Kim S-Y, Jeong B-H, Chang B, Shin SJ, Koh W-J. Severe vitamin D deficiency is associated with non-tuberculous mycobacterial lung disease: a case-control study. *Respirology* 2013; 18:983–988.
7 Hall WB, Sparks AA, Aris RM. Vitamin d deficiency in cystic fibrosis. *Int J Endocrinol* 2010;2010:218691 10.1155/2010/218691.
8 Knapp EA, Fink AK, Goss CH, Sewall A, Ostrenga J, Dowd C, *et al*. The cystic fibrosis foundation patient registry: design and methods of a national observational disease registry. *Ann Am Thorac Soc* 2016;13: 1173–1179.
9 Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, *et al*.; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96:1911–1930.
10 Tangpricha V, Kelly A, Stephenson A, Maguiness K, Enders J, Robinson KA, *et al*.; Cystic Fibrosis Foundation Vitamin D Evidence-Based Review Committee. An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the Cystic Fibrosis Foundation. *J Clin Endocrinol Metab* 2012;97:1082–1093.
11 Floto A, Olivier KN, Saiman L, Daley CL, Herrmann J-L, Nick JA, *et al*. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. *Thorax* 2016;71:i1–i22.

Optimal Respiratory Assistance Strategy for Patients with COVID-19

To the Editor:

We read with interest the study by Gershengorn and colleagues on the impact of high flow nasal cannula (HFNC) use on clinical outcomes and allocation of invasive mechanical ventilators (IMVs) among patients with coronavirus disease (COVID-19) related acute hypoxemic respiratory failure (AHRF) (1). The authors apply computer simulation to determine the utility of HFNC as part of several treatment strategies in improving outcomes and invasive mechanical ventilator availability. The authors conclude that the best strategy is one that employs early intubation of patients who do not need IMV urgently but incorporates HFNC oxygen therapy when mechanical ventilator inventory falls below 10% of capacity. Although incorporating HFNC oxygen therapy into the treatment of patients with COVID- 19 related respiratory failure makes intuitive and scientific sense, we question the promotion of early intubation for patients who do not require such intervention at the time of initial assessment.

The authors define "nonurgent" patients as those clinicians would feel are at high risk of needing IMV but do not need it urgently. These are the patients who would be managed with alternative means of respiratory assistance such as noninvasive ventilation (NIV) and HFNC oxygen treatment in practice and also in clinical trials. Consequently, by definition, we have no outcome data on how such patients would have done had they been