Title

Early acquisition and conversion of Pseudomonas aeruginosa in Hispanic youth with cystic fibrosis in the United States.

Journal

Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 20(3)

ISSN

1569-1993

Authors

McGarry, Meghan E
Huang, Chiung-Yu
Nielson, Dennis W
et al.

Publication Date

2021-05-01

DOI

10.1016/j.jcf.2020.10.002

Peer reviewed

HHS Public Access

Author manuscript

J Cyst Fibros. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

J Cyst Fibros. 2021 May ; 20(3): 424–431. doi:10.1016/j.jcf.2020.10.002.

Early Acquisition And Conversion Of Pseudomonas aeruginosa In Hispanic Youth With Cystic Fibrosis In the United States

Meghan E. McGarry, M.D., M.A.S.[1], **Chiung-Yu Huang, Ph.D.**[2], **Dennis W. Nielson, M.D., Ph.D.**[1], **Ngoc P. Ly, M.D., M.P.H.**[1]

[1]:Department of Pediatrics, University of California, San Francisco

[2]:Department of Epidemiology and Biostatistics, University of California, San Francisco

Abstract

Background: For unknown reasons, Hispanic patients with cystic fibrosis (CF) have more severe pulmonary disease than non-Hispanic white patients. In CF, the pulmonary pathogen *Pseudomonas aeruginosa* is associated with worse outcomes. We sought to determine if Hispanic patients with CF are at an increased risk of acquiring *P. aeruginosa* or acquire it earlier than non-Hispanic white patients.

Methods: This is a longitudinal study comparing the timing and risk of acquisition of different forms of *P. aeruginosa* between Hispanic and non-Hispanic white patients aged 0-21 years old with CF in the CF Foundation Patient Registry (CFFPR) in 2008-2013. The age at the initial acquisition of P. aeruginosa (initial acquisition, mucoid, chronic, multidrug-resistant) was summarized using Kaplan-Meier survival curves and analyzed using Cox proportional hazards regression models.

Results.—Of 10,464 patients, 788 (7.5%) were Hispanic and 9,676 (92.5%) were non-Hispanic white. Hispanic patients acquired all forms of *P. aeruginosa* at a younger age than non-Hispanic white patients. Hispanic patients had a higher risk of acquiring *P. aeruginosa* than non-Hispanic white patients: the hazard ratio (HR) was 1.26 (95% CI 1.16-1.38, p<0.001) for initial *P. aeruginosa*, 1.59 (95% CI 1.43-1.77, p<0.001) for mucoid *P. aeruginosa*, 1.91 (95% CI 1.64-2.23, p<0.001) for multidrug-resistant *P. aeruginosa*, and 1.39 (95% CI 1.25-1.55, p<0.001) for chronic *P. aeruginosa.*

Corresponding Author: Meghan E McGarry, MD MAS, 550 16th Ave, Box 0632, San Francisco, CA 94158, Meghan.McGarry@ucsf.edu, Phone: 415-476-3334. Fax: 415-476-9278.

Contributors' Statements:

Meghan McGarry: Conceptualization, Methodology, Data curation, writing original draft, Visualization, Funding acquisition **Chiung-Yu Huang**: Methodology, Software, Formal analysis, Writing- review and editing, Visualization **Dennis Nielson**: Writing- review and editing **Ngoc Ly**: Conceptualization, Writing- review and editing, Supervision

Competing of Interests

All authors have no competing interests to declare.

Conclusions: Hispanic patients have an increased risk of acquiring *P. aeruginosa* and acquire it at an earlier age than non-Hispanic white patients in the United States. This may contribute to increased morbidity and mortality in Hispanic patients with CF.

Keywords

Pseudomonas aeruginosa; Cystic Fibrosis; Health disparities

While there have been significant advances in the care of and outcomes in cystic fibrosis (CF), not all groups have benefited equally. Hispanic patients with CF have increased mortality and more severe pulmonary disease than non-Hispanic white patients with CF(1–4). The ethnic differences in pulmonary function and mortality are not uniform across the United States(2, 3). It is not yet known why Hispanic patients with CF have worse outcomes, in particular, more severe pulmonary disease.

Respiratory infections are a leading cause of lung disease in CF, and *Pseudomonas aeruginosa* is one of the most common respiratory pathogens(5). *Pseudomonas aeruginosa* is a major predictor of both morbidity and mortality in CF. Patients with *P. aeruginosa* have a 2.6 times higher risk of death than those free of *P. aeruginosa(6). Pseudomonas aeruginosa* is associated with greater reduction and a more rapid decline in pulmonary function after acquisition(6, 7). Some types of *P. aeruginosa* are associated with increased severity pulmonary disease. Acquiring or converting to mucoid or multidrug-resistant forms of P. aeruginosa leads to more severe disease with accelerated decline in pulmonary function(8) and increased mortality(9). Conversion from intermittently positive cultures to chronic *P. aeruginosa* also has more severe impact on lung disease. Acquisition of any type of *P. aeruginosa* at an earlier age has a worse prognosis(10).

The epidemiology of *P. aeruginosa* acquisition has been well-described in the general CF population, however, ethnic differences in the timing of acquisition and conversion of *P. aeruginosa* has not been investigated in longitudinal studies. Prior cross-sectional analyses found an earlier age of acquisition of *P. aeruginosa* but no difference in *P. aeruginosa* incidence in Hispanic patients compared to non-Hispanic patients(11, 12). In California, Hispanic patients first acquired *P. aeruginosa* at an earlier median age than non-Hispanic white patients (3.7 vs. 4.6 years)(12). A cross-sectional analysis of patients in the U.S. in 2004 also found that Hispanic patients first acquired *P. aeruginosa* at an earlier mean age than non-Hispanic white patients (6.6 vs. 9.9 years old)(11). In a mortality analysis of adults with CF, fewer Hispanic patients acquired *P. aeruginosa* than non-Hispanic white patients (44.2% vs. 48.2%)(3). Our group had previously found that more Hispanic youth were *P. aeruginosa* positive compared to non-Hispanic white youth (39.9% vs. 33.8%) and this difference varied across U.S. Census Regions(2). Differences in the timing of *P. aeruginosa* infections may contribute to increased morbidity and mortality in Hispanic patients with CF. We hypothesize that Hispanic patients with CF are at increased risk of acquiring *P. aeruginosa* and of converting to more severe forms of *P. aeruginosa.* Using a longitudinal pediatric CF study, we sought to determine if the risk and timing of acquisition and conversion of *P. aeruginosa* vary between Hispanic and non-Hispanic White patients with CF in the United States.

Methods

Study Population:

The U.S. Cystic Fibrosis Foundation Patient Registry is a retrospective observational registry study of patients from accredited CF centers which includes approximately 81-84% of patients with CF in the United States(13). All patients were <22 years old, diagnosed with CF, and included in the U.S. Cystic Fibrosis Foundation Patient Registry (CFFPR) between 2008 to 2013.

Overall Design:

We performed a longitudinal study of Hispanic and non-Hispanic white patients to examine ethnic differences in the age at *P. aeruginosa* acquisition and risk of acquisition of *P. aeruginosa.* Respiratory microbiologic cultures were collected when clinically indicated at accredited CF centers and recorded in the CFFPR as encounter-level data. Respiratory cultures are recommended to be routinely collected at least quarterly and are typically collected when patients have new or increased respiratory symptoms in accordance with Cystic Fibrosis Foundation consensus guidelines(14).

The primary predictor was self-identified race and ethnicity, defined as Hispanic or non-Hispanic white. Other races and ethnicities were excluded.

The primary outcome was the age at first positive culture (acquisition) of any form of *P. aeruginosa* respiratory infection defined as initial *P. aeruginosa.* The secondary outcomes the age at first positive culture (acquisition) of mucoid *P. aeruginosa*, multidrug-resistant *P. aeruginosa*, and chronic *P. aeruginosa*, all of which are associated with more severe pulmonary disease. Chronic *P. aeruginosa* was defined using the modified Leeds criteria as when 3 or more respiratory cultures were provided in a 2-year period and ≥50% or more were positive for *P. aeruginosa(15, 16).* If only 2 cultures were provided, both must be positive. The time of acquisition of chronic *P. aeruginosa* is the first culture positive in the 2-year period. Time to conversion from intermittent *P. aeruginosa* to chronic *P. aeruginosa* was examined, which was defined as the time from the first positive culture until the time when first considered to have *P. aeruginosa.* We then examined the correlation of the three subtypes of *P. aeruginosa* (mucoid, chronic, multidrug-resistant) with each other.

As socioeconomic status (SES) factors can be important in understanding health disparities, we did a sensitivity analysis comparing the addition of maternal education, paternal education, annual income, and insurance status in our primary model. Maternal and paternal education was defined as high school or less, some college or more, or missing. Insurance status was defined as Medicaid regardless of secondary insurance listed, no Medicaid, or no insurance. Annual income was defined as <$50,000, $50,000-90,000, >$90,000, or missing

Statistical Methods:

The events of interest are different forms of *P. aeruginosa* (initial acquisition, mucoid, chronic, multidrug-resistant). To assess the risk of acquisition over age, separate time-to-event analysis was performed for each form of *P. aeruginosa* where the time origin was set to

be date of birth and the censoring time was defined as the last CFFPR encounter or 22 years of age. The Kaplan-Meier curves were used to summarize the age of initial acquisition for each form of *P. aeruginosa* with the log-rank test and in addition, the event-free probabilities at 2.5 and 5.0 years old were compared between Hispanic and non-Hispanic white patients using the Wald-type tests. Cox proportional hazards models were used to evaluate the difference in risk for acquiring each form of *P. aeruginosa* between ethnicities. All analyses were adjusted for the following covariates that were chosen *a priori* based on prior literature that may be associated with ethnicity and/or *P. aeruginosa* acquisition: sex, CF-related diabetes, pancreatic insufficiency (pancreatic enzyme replacement therapy use or none), CFTR mutation class severity (Class I-III, Class IV-V, Unclassified)(17), age of entry into CFFPR, U.S. Census Region at time of enrollment (West, Midwest, Northeast, South), year of birth, number of cultures in prior year (4+ or <4), and underweight (using weight-for-length, body mass index),. Age of entry into CFFPR was chosen as it accounts for the fact that those who enrolled at an older age will have an older age at first positive *P. aeruginosa* test after entering the CFFPR. To account for changing prevalence of *P. aeruginosa* in the CF population over time, we included year of birth in our models. The following covariates were entered as time-dependent variables: pancreatic insufficiency, CF-related diabetes, and underweight. A sensitivity analysis was conducted with the inclusion of maternal education (no college vs. any college), paternal education (no college vs. any college), time-dependent annual income (<$50,000, $50,000-90,000, vs. >$90,0000) and time-dependent insurance status (private insurance, no insurance, vs. no insurance) added to the main model. There was missing data for the following variables: maternal education, paternal education, insurance status, and annual income. A separate category for "missing" was created for each of these variables when added to the SES sensitivity analysis. Subject characteristics were compared between those with and without missing data in supplemental material (Supplemental Tables 1–2). We examined the correlation of the three subtypes of *P. aeruginosa* (mucoid, chronic, multidrug-resistant) by including each subtype as time-dependent risk factor into the model for risk of acquisition of the other subtypes of *P. aeruginosa.*

Ethnic differences in clinical characteristics and demographics at time of study entry were compared using Chi-squared tests for categorical variables and Student *t* tests for continuous variables. A 2-sided P-value <0.05 was considered statistically significant. Statistical analysis was performed in R 3.6.2 (R Core Team 2019). The study was approved by the University of California, San Francisco Institutional Review Board (15-17491) and the CF Foundation Registry/Comparative Effectiveness Research Committee.

Results

Characteristics of the Study Population

Of 10,464 patients with CF, 788 (7.5%) were Hispanic and 9,676 (92.5%) were non-Hispanic white (Table 1). Hispanic patients were more likely to be pancreatic sufficient (4.9% vs. 3.1%). The proportion of patients in each CFTR mutation severity class varied by ethnicity: non-Hispanic white patients are more likely to have severe mutations (Class I-III) while Hispanic patients are more likely to have mild mutations (Class IV-V) or mutations

that are unknown/unclassified. Hispanic patients were slightly younger at the time of enrollment into the CFFPR (median 0.74 vs. 0.89 years old, p<0.001). There was no difference in the prevalence of CF-related diabetes or being underweight. Hispanic patients were less likely to have maternal education of at least some college (48.1% vs. 64.9%) and less likely to have private insurance (39.3% vs. 58.3%). The Midwest had the lowest percentage of Hispanic patients (2.4%) and the West had the highest percentage of Hispanic patients (16.2%).

Respiratory cultures

There was a total of 398,656 bacterial respiratory cultures done in non-Hispanic white patients and 28,848 in Hispanic patients. Hispanic patients had an average of 3.0 cultures annually compared to 2.7 cultures annually in non-Hispanic white patients. There was no difference in the timing of the first respiratory culture was performed at slightly earlier age in Hispanic patients compared to non-Hispanic white patients (median 1.6 vs. 1.7 years old). Non-Hispanic white patients had an average observation of 19.0 years as compared to 17.0 years in Hispanic patients with all data truncated after 21 years old.

Overall, 682 of 788 (86.5%) Hispanic patients and 8570 of 9676 (88.6%) of non-Hispanic white patients acquired *P.* aeruginosa. Mucoid *P.* aeruginosa was acquired by 393 of 788 (49.9%) of Hispanic patients and 4460 of 9676 (46.1%) of non-Hispanic white patients. Chronic *P.* aeruginosa was acquired by 425 of 788 (53.9%) of Hispanic patients and 5366 of 9676 (55.5%) of non-Hispanic white patients. Multidrug-resistant *P.* aeruginosa was acquired by 196 of 788 (24.9%) of Hispanic patients and 1622 of 9676 (16.8%) of non-Hispanic white patients.

Age at Acquisition

Hispanic patients acquired *P.* aeruginosa at a younger age than non-Hispanic white patients based on the estimated Kaplan-Meier curves: initial *P.* aeruginosa (median 5.6 vs. 7.3 years), mucoid *P.* aeruginosa (median 16.4 vs. 19.9 years), and chronic *P.* aeruginosa (median 15.0 vs. 16.7 years). The median age of multidrug-resistant *P.* aeruginosa cannot be determined as neither group reached 50% of patients acquiring multidrug-resistant *P.* aeruginosa.

Risk of Acquiring Pseudomonas

Hispanic patients had a higher risk than non-Hispanic white patients of acquiring all forms of *P.* aeruginosa (Figures 1–4). Compared to non-Hispanic white patients, Hispanic patients had a 1.26 times higher risk (95% CI 1.16-1.38, p<0.001) in acquiring initial *P.* aeruginosa, 1.59 times higher risk of acquiring mucoid *P. aeruginosa* than non-Hispanic white patients (95% CI 1.43-1.77, p<0.001), and 1.91 times higher risk of acquiring multidrug-resistant *P. aeruginosa* (95% CI 1.64-2.23, p<0.001) (see Supplementary Material). Hispanic patients were more likely to have chronic *P. aeruginosa* at the time of first positive culture and never have intermittent *P. aeruginosa* (33.0% vs. 30.3%, p<0.001). There was a 1.39 times higher risk of having chronic *P. aeruginosa* in Hispanic patients compared to non-Hispanic white patients (95% CI 1.25-1.55, p<0.001). Hispanic patients had a shorter median duration of intermittent *P. aeruginosa* than white patients (4.8 years vs. 5.6 years) and were at 1.34 times higher risk for converting from intermittent to chronic *P. aeruginosa* (95% CI 1.20-1.49,

p<0.001; Figure 5). At the age of 2.5 years old, there were statistically significant differences between ethnicities in risk of acquiring any, mucoid, and chronic *P. aeruginosa* (Table 2). At 5 years old, there was a statistically significant difference between ethnicities in risk of acquiring multidrug-resistant *P. aeruginosa.*

Pseudomonas Subtype Associations

To evaluate association between a selected pair of pseudomonas subtypes, we performed Cox regression with acquisition of one of the subtypes as a time-dependent covariate, while treating the other subtype as the event of interest, ethnicity and other covariates. Compared to those who did not have chronic *P. aeruginosa*, patients who had chronic *P. aeruginosa* had a 4.51 times higher risk of mucoid *P. aeruginosa.* (95% CI 4.25-4.79, p<0.001) and 6.40 times higher risk of multidrug-resistant *P. aeruginosa* (95% CI 5.60.-7.31, p<0.001). Patients with mucoid *P. aeruginosa* had a 5.89 times higher risk of multidrug-resistant *P. aeruginosa* (95% CI 5.25-6.62, p<0.001). There were no significant differences between Hispanic and non-Hispanic white patients in any of the associations of *P. aeruginosa* subtypes.

Sub-analyses by Socioeconomic Status

With inclusion of measures of socioeconomic status (insurance status, annual income, paternal education, and maternal education) into our analyses, compared to non-Hispanic white patients, there was a slightly decreased risk of all forms of *P. aeruginosa* for Hispanic patients (Table 3). Maternal education was missing for 14.8% of Hispanic patients and 15.1% of non-Hispanic white patients. Paternal education was missing for 17.3% of Hispanic patients and 16.0% of non-Hispanic white patients, Income was missing for 52.0% of Hispanic patients and 39.1% of non-Hispanic white patients, Insurance status was only missing for 1 non-Hispanic white patient (0%) and 0 Hispanic patients.

Full unadjusted and adjusted models for all analyses are included in supplemental material (Supplement Tables 3–4).

Discussion

Using the largest database of Hispanic patients with CF, we found that Hispanic patients were at an increased risk as compared to non-Hispanic white patients of acquiring *P. aeruginosa*, a serious pulmonary pathogen that contributes to pulmonary disease severity. In longitudinal analysis, we found that the difference between ethnicities in risk of acquisition of *P. aeruginosa* was not equal for all forms. Hispanic patients had a significantly higher risk for acquiring the more severe forms: mucoid and multidrug-resistant *P. aeruginosa.* Hispanic patients converted from intermittent to chronic *P. aeruginosa* in a shorter time period than non-Hispanic white patients and were more likely to convert from intermittent to chronic *P. aeruginosa.* This is the first longitudinal study to our knowledge showing that Hispanic patients with CF are at increased risk of *P. aeruginosa* pulmonary infections.

Not only were Hispanic patients at an increased risk of *P. aeruginosa* acquisition, but they acquired all forms of *P. aeruginosa* at an earlier age than non-Hispanic white patients. Hispanic patients were at an increased risk of *P. aeruginosa* than non-Hispanic white patients beginning very early in childhood: by 2.5 years old for initial, mucoid, and chronic *P.*

aeruginosa and by 5 years old for multidrug-resistant *P. aeruginosa.* This complements prior cross-sectional studies which showed Hispanic children acquire *P. aeruginosa* at a younger age than non-Hispanic white patients(11, 12) and our prior work which showed more Hispanic children acquire *P. aeruginosa*(2). Early *P. aeruginosa* acquisition, in particular before age 5 years old, is strongly associated with severe pulmonary disease later in life(18). We have previously found that Hispanic patients with CF have more severe pulmonary function than non-Hispanic white patients at 6 years old, the time pulmonary function can be first accurately measured(1, 2). Early acquisition of *P. aeruginosa* in Hispanic patients may lead to the observed more severe pulmonary function. However, Hispanic patients may already have more severe pulmonary disease putting them at higher risk for *P. aeruginosa*, as pulmonary function is not measured before 6 years old.

Our findings of increased risk of *P. aeruginosa* and earlier age of acquisition complements prior literature showing that Hispanic patients suffer an increased burden from their disease than do non-Hispanic white patients with CF. Hispanic patients not only have more severe pulmonary disease(1, 2) but also increased mortality(3, 12). Pulmonary infections, including *P. aeruginosa*, are strongly associated with both morbidity and mortality in CF(6, 7). We found that *P. aeruginosa* acquisition in Hispanic patients varied from non-Hispanic white patients in all three ways we examined: 1) overall increased risk, 2) risk increased with more severe forms, and 3) earlier age of acquisition with all forms. Given that it is not known why Hispanic patients have increased morbidity and mortality, it is possible that both the increased risk and earlier age of *P. aeruginosa* acquisition may be contributing factors. The contributions of timing and type *P. aeruginosa* acquisition to pulmonary disease and mortality in Hispanic patients will need to be further investigated.

It is unknown why Hispanic patients not only acquire all forms of *P. aeruginosa* at a younger age but are also at increased risk of acquisition of *P. aeruginosa.* It may be driven by differences in climate, environmental exposures, CFTR mutations, genetic modifiers, use or response to anti-pseudomonal therapies, or socioeconomic status (SES). Although SES is important in understanding health inequalities in Hispanic patients(19), including measurements of SES did not significantly change our findings. While SES is associated with severe pulmonary disease and increased mortality in CF, household income and maternal education have not been clearly associated with *P. aeruginosa* acquisition(20). There are limited markers of SES collected by the CFFPR and those SES variables collected, such as maternal education, have missing data due to inconsistent reporting across CF centers, which is a limitation to our findings. There are possibly other SES factors that could differentially increase risk of *P. aeruginosa* acquisition for Hispanic patients(19).

Our findings add to the body of evidence that Hispanic patients have more severe disease from CF even though they have disease characteristics, such as mild CFTR genetic mutations and higher BMI, that are typically associated with better outcomes. This is in stark contrast to the general U.S. population where Hispanic persons have a longer life expectancy than white persons. This paradox is also seen in other pediatric pulmonary diseases such as asthma where Hispanic children have worse outcomes compared to white children(21). The observed disparities may be driven by factors that specifically affect Hispanic patients(19).

Further investigation is needed to understand why Hispanic patients are at increased risk of *P. aeruginosa.* This includes exploring genetic differences or environmental exposures, such as air pollution, that may result in our observed findings. There needs to be exploration in the treatment of *P. aeruginosa* in Hispanic patients, including if anti-pseudomonal antibiotics are equally effective in all patients. Minority patients were either not included or under-represented in anti-pseudomonal studies(22). Understanding how differences in *P. aeruginosa* in Hispanic patients contribute to increased morbidity and more severe pulmonary disease is vital to improve outcomes. Clinicians should be aware that Hispanic patients are at increased risk of *P. aeruginosa* and address any barriers to treatment adherence low health literacy or language may cause. This vulnerable patient population deserves increased attention to ensure the best possible health outcomes.

Limitations:

One limitation in our study is there was not a standard interval for the respiratory culture sampling as this was observational data from the CFFPR. Respiratory cultures were done when clinically indicated. The CF Foundation recommendation is to have a respiratory culture at least 4 times a year(23), but the average number of cultures for both groups was less than that. Hispanic patients had slightly more cultures annually compared to non-Hispanic white patients, which could mean that Hispanic patients were picked up earlier due to more frequent culturing but there may be no actual difference in timing of *P. aeruginosa* acquisition. This is unlikely to fully explain our findings since there was a few years difference in acquisition and there was only a small difference in the number of cultures annually. Hispanic patients may have more frequent cultures due to having more respiratory symptoms and worse pulmonary disease as demonstrated by higher rates of mucoid and MDR pseudomonas by 5 years of age.

Another limitation of our study is that respiratory cultures can be from either the upper airway (posterior pharyngeal culture) or the lower airways (BAL, sputum). There are varying sensitivity and specificity for *P. aeruginosa* based on the type of sample. Upper airway cultures without *P. aeruginosa* are unlikely to have *P. aeruginosa* in the lower airway(24). However, upper airway cultures that are positive for *P. aeruginosa* are less accurate in predicting lower airway *P. aeruginosa(24).*

Our findings are based on data from the U.S CFFPR and thus only apply to Hispanic patients in the United States. Our findings may not apply to Hispanic patients residing in other countries.

Despite these limitations, out study using real-life data demonstrated that Hispanic patients in the United States have an increased risk of developing *P. aeruginosa* and develop all forms at an earlier age than white patients. The increased incidence and earlier age of onset of *P. aeruginosa* may contribute to the increased morbidity and mortality in Hispanic youth with CF. Our findings add to the body of literature showing Hispanic patients are a vulnerable sub-population of the U.S. CF community.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to thank the Cystic Fibrosis Foundation for the use of the CF Foundation Patient Registry data to conduct this study. Additionally, we would like to thank the patients, care providers, and care coordinators at CF centers throughout the United States for their contributions to the CF Foundation Patient Registry.

Funding

This work was supported by the National Heart, Lung, and Blood Institute [1K23HL133437-01A1, UG1HL139106, U10HL109146–01], the Cystic Fibrosis Foundation Therapeutics [MCGARR16A0], the National Institute of Diabetes and Digestive and Kidney [P30 DK072517], the Cystic Fibrosis Foundation [LY18Y0, CC029-18]].

Glossary

CFFPR	CF Foundation Patient Registry

References

1. McGarry ME, Neuhaus J, Nielson DW, Burchard EG, Ly NP. Pulmonary function disparities exist and persist in Hispanic patients with cystic fibrosis: A longitudinal analysis. Pediatric pulmonology. 2017;52(12):1550–7. [PubMed: 29082671]
2. McGarry ME, Neuhaus JM, Nielson DW, Ly NP. Regional variations in longitudinal pulmonary function: A comparison of Hispanic and non-Hispanic subjects with cystic fibrosis in the United States. Pediatric pulmonology. 2019.
3. Rho J, Ahn C, Gao A, Sawicki GS, Keller A, Jain R. Disparities in Mortality of Hispanic Cystic Fibrosis Patients in the United States: A National and Regional Cohort Study. American journal of respiratory and critical care medicine. 2018(ja).
4. McColley SA, Schechter MS, Morgan WJ, Pasta DJ, Craib ML, Konstan MW. Risk factors for mortality before age 18 years in cystic fibrosis. Pediatric pulmonology. 2017;52(7):909–15. [PubMed: 28436621]
5. LiPuma JJ. The changing microbial epidemiology in cystic fibrosis. Clinical microbiology reviews. 2010;23(2):299–323. [PubMed: 20375354]
6. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatric pulmonology. 2002;34(2):91–100. [PubMed: 12112774]
7. Kosorok MR, Zeng L, West SE, Rock MJ, Splaingard ML, Laxova A, et al. Acceleration of lung disease in children with cystic fibrosis after Pseudomonas aeruginosa acquisition. Pediatric pulmonology. 2001;32(4):277–87. [PubMed: 11568988]
8. Demko CA, Byard PJ, Davis PB. Gender differences in cystic fibrosis: Pseudomonas aeruginosa infection. Journal of clinical epidemiology. 1995;48(8): 1041–9. [PubMed: 7775991]
9. Henry RL, Mellis CM, Petrovic L. Mucoid Pseudomonas aeruginosa is a marker of poor survival in cystic fibrosis. Pediatric pulmonology. 1992; 12(3):158–61. [PubMed: 1641272]
10. Hudson VL, Wielinski CL, Regelmann WE. Prognostic implications of initial oropharyngeal bacterial flora in patients with cystic fibrosis diagnosed before the age of two years. The Journal of pediatrics. 1993;122(6):854–60. [PubMed: 8501559]
11. Watts KD, Seshadri R, Sullivan C, McColley SA. Increased prevalence of risk factors for morbidity and mortality in the US Hispanic CF population. Pediatric pulmonology. 2009;44(6):594–601. [PubMed: 19437506]
12. Buu MC, Sanders LM, Mayo JA, Milla CE, Wise PH. Assessing differences in mortality rates and risk factors between Hispanic and non-Hispanic patients with cystic fibrosis in California. CHEST Journal. 2016;149(2):380–9.

13. 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. Annals of the American Thoracic Society. 2016;13(7):1173–9. [PubMed: 27078236]

14. Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. The Journal of pediatrics. 2008;153(2):S4–S14. [PubMed: 18639722]

15. Crull MR, Ramos KJ, Caldwell E, Mayer-Hamblett N, Aitken ML, Goss CH. Change in Pseudomonas aeruginosa prevalence in cystic fibrosis adults over time. BMC pulmonary medicine. 2016;16(1):176. [PubMed: 27927212]

16. Crull MR, Somayaji R, Ramos KJ, Caldwell E, Mayer-Hamblett N, Aitken ML, et al. Changing rates of chronic Pseudomonas aeruginosa infections in cystic fibrosis: a population-based cohort study. Clinical Infectious Diseases. 2018;67(7):1089–95. [PubMed: 29534149]

17. De Gracia J, Mata F, Alvarez A, Casals T, Gatner S, Vendrell M, et al. Genotype-phenotype correlation for pulmonary function in cystic fibrosis. Thorax. 2005;60(7):558–63. [PubMed: 15994263]

18. Pittman JE, Calloway EH, Kiser M, Yeatts J, Davis SD, Drumm ML, et al. Age of Pseudomonas aeruginosa acquisition and subsequent severity of cystic fibrosis lung disease. Pediatric pulmonology. 2011;46(5):497–504. [PubMed: 21194167]

19. McGarry ME, Williams WA, McColley SA. The demographics of adverse outcomes in cystic fibrosis. Pediatric pulmonology. 2019;54:S74–S83. [PubMed: 31715087]

20. Rosenfeld M, Emerson J, McNamara S, Thompson V, Ramsey BW, Morgan W, et al. Risk factors for age at initial Pseudomonas acquisition in the cystic fibrosis epic observational cohort. Journal of Cystic Fibrosis. 2012;11(5):446–53. [PubMed: 22554417]

21. Canino G, Koinis-Mitchell D, Ortega AN, McQuaid EL, Fritz GK, Alegría M. Asthma disparities in the prevalence, morbidity, and treatment of Latino children. Social science & medicine. 2006;63(11):2926–37. [PubMed: 16956704]

22. McGarry ME, McColley SA. Minorities are underrepresented in clinical trials of pharmaceutical agents for cystic fibrosis. Annals of the American Thoracic Society. 2016;13(10):1721–5. [PubMed: 27410177]

23. Lahiri T, Hempstead SE, Brady C, Cannon CL, Clark K, Condren ME, et al. Clinical practice guidelines from the cystic fibrosis foundation for preschoolers with cystic fibrosis. Pediatrics. 2016;137(4):e20151784. [PubMed: 27009033]

24. Burns JL, Gibson RL, McNamara S, Yim D, Emerson J, Rosenfeld M, et al. Longitudinal assessment of Pseudomonas aeruginosa in young children with cystic fibrosis. The Journal of infectious diseases. 2001;183(3):444–52. [PubMed: 11133376]

Highlights:

- Hispanics are at higher risk of acquiring *P. aeruginosa* than non-Hispanic whites
- Hispanics acquire *P. aeruginosa* at an earlier age than non-Hispanic whites
- Hispanics are at higher risk for severe forms: mucoid, chronic, multidrug resistant

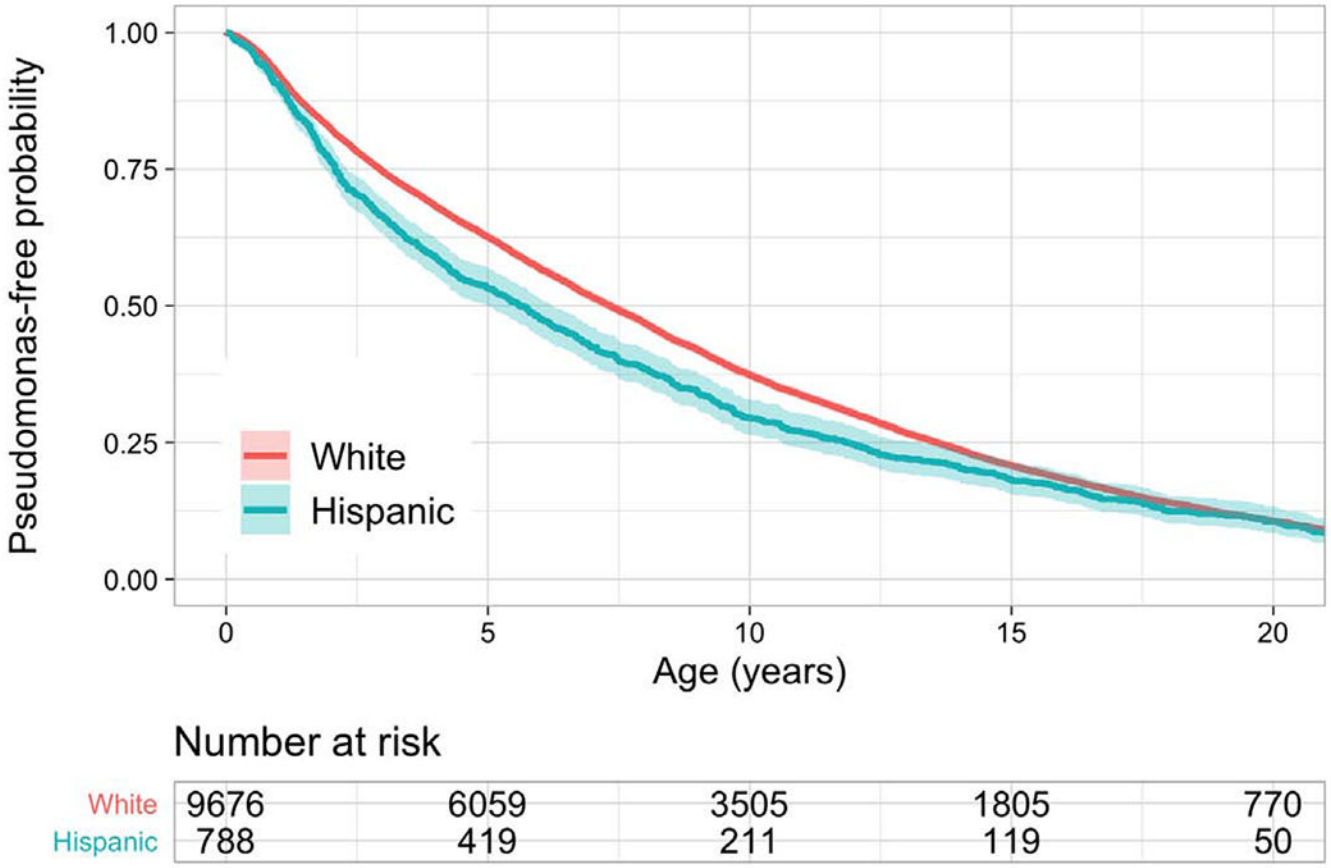

Figure 1: Kaplan-Meier Curves for the Risk of First Acquisition of Any Type of Pseudomonas By Ethnicity

Hispanic patients acquired *P. aeruginosa* at 5.6 years old compared to 7.3 years old in non-Hispanic white patients. Compared to non-Hispanic white patients, Hispanic patients had a 1.26 times higher risk (95% CI 1.16-1.38, p<0.001) in acquiring initial *P. aeruginosa*,, adjusted for sex, CF-related diabetes, pancreatic insufficiency, CFTR mutation class, age of entry into CF Foundation Patient Registry, US Census Region, year of birth, number of cultures, and underweight.

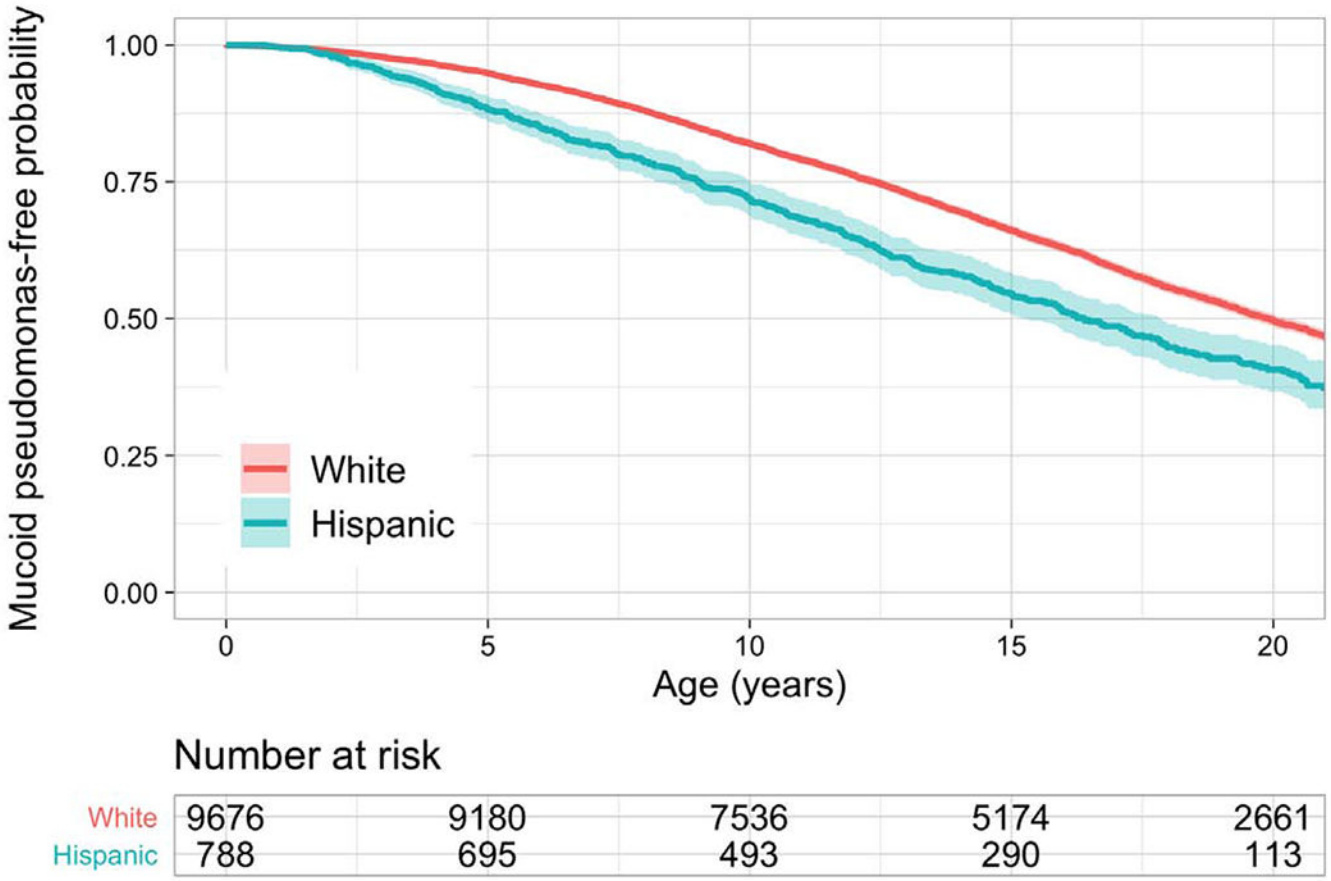

Figure 2: Kaplan-Meier Curves for the Risk of Acquisition of Mucoid Pseudomonas By Ethnicity

The median age at acquisition was 16.4 years old in Hispanic patients and 19.9 years old in non-Hispanic white patients. Compared to non-Hispanic white patients, Hispanic patients had a 1.59 times higher risk of acquiring mucoid *P. aeruginosa* (95% CI 1.43-1.77, p<0.001) adjusted for sex, CF-related diabetes, pancreatic insufficiency, CFTR mutation class, age of entry into CF Foundation Patient Registry, US Census Region, year of birth, number of cultures, and underweight.

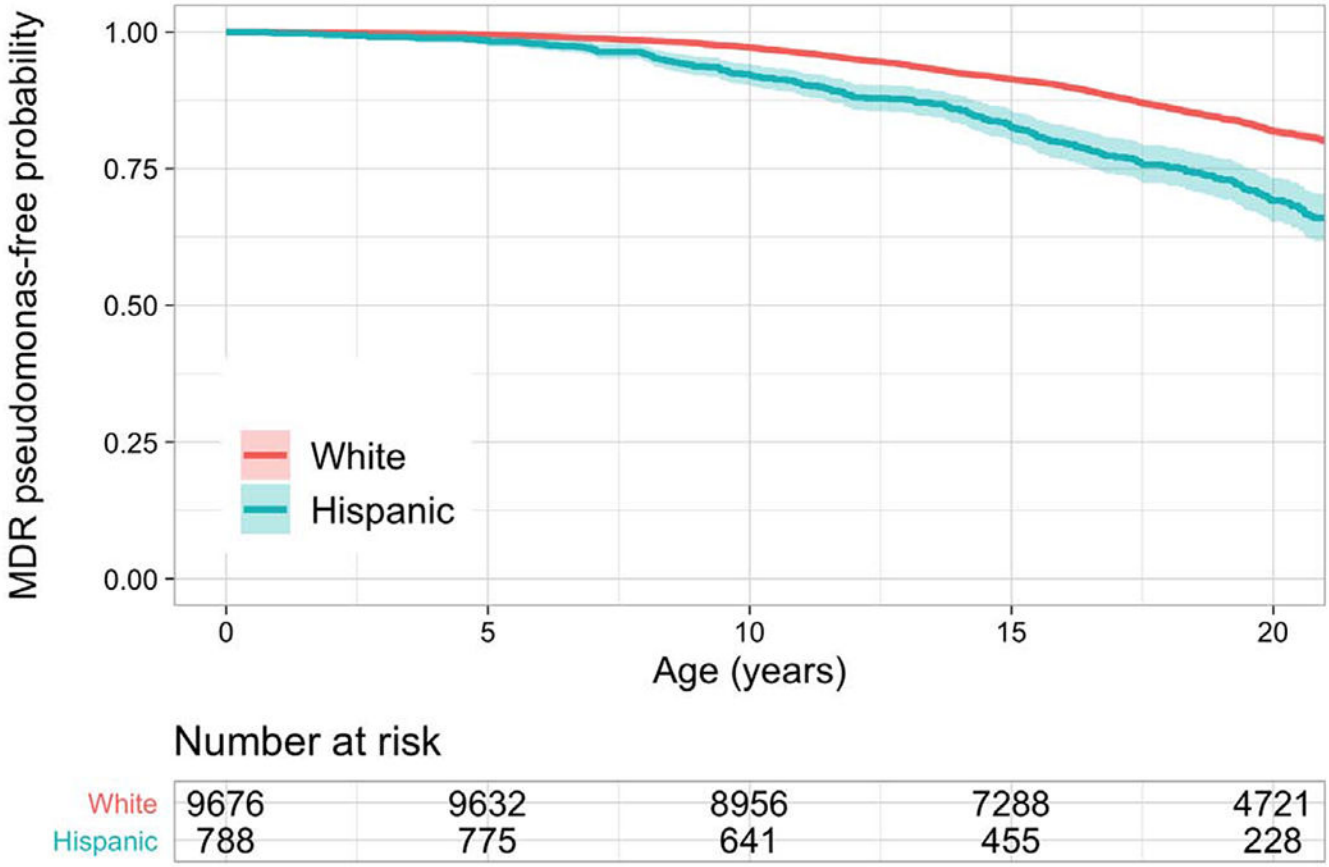

Figure 3: Kaplan-Meier Curves for the Risk of Acquisition of Multidrug Resistant Pseudomonas By Ethnicity

Compared to non-Hispanic white patients, Hispanic patients had a 1.91 times higher risk of acquiring multidrug-resistant *P. aeruginosa* (95% CI 1.64-2.23, p<0.001), adjusted for sex, CF-related diabetes, pancreatic insufficiency, CFTR mutation class severity, age of entry into CF Foundation Patient Registry, US Census Region, year of birth, number of cultures, and underweight.

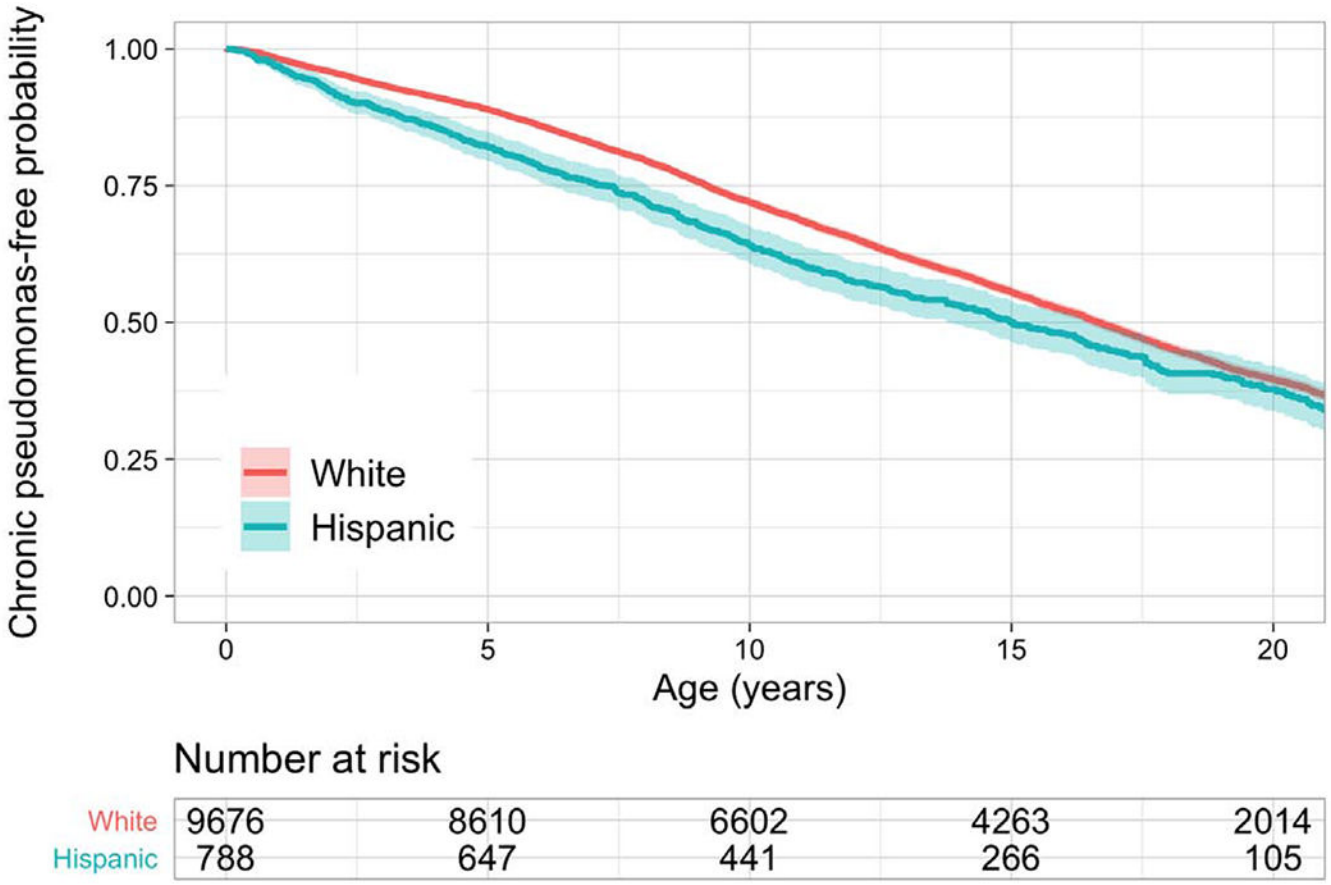

Figure 4: Kaplan-Meier Curves for the Risk of Acquisition of Chronic Pseudomonas By Ethnicity

The median age at acquisition was 15.0 years old in Hispanic patients and 16.7 years in non-Hispanic white patients. Compared to non-Hispanic white patients, there was a 1.39 times higher risk of having chronic *P. aeruginosa* in Hispanic patients (95% CI 1.25-1.55, p<0.001), adjusted for sex, CF-related diabetes, pancreatic insufficiency, CFTR mutation class, age of entry into CF Foundation Patient Registry, US Census Region, year of birth, number of cultures, and underweight.

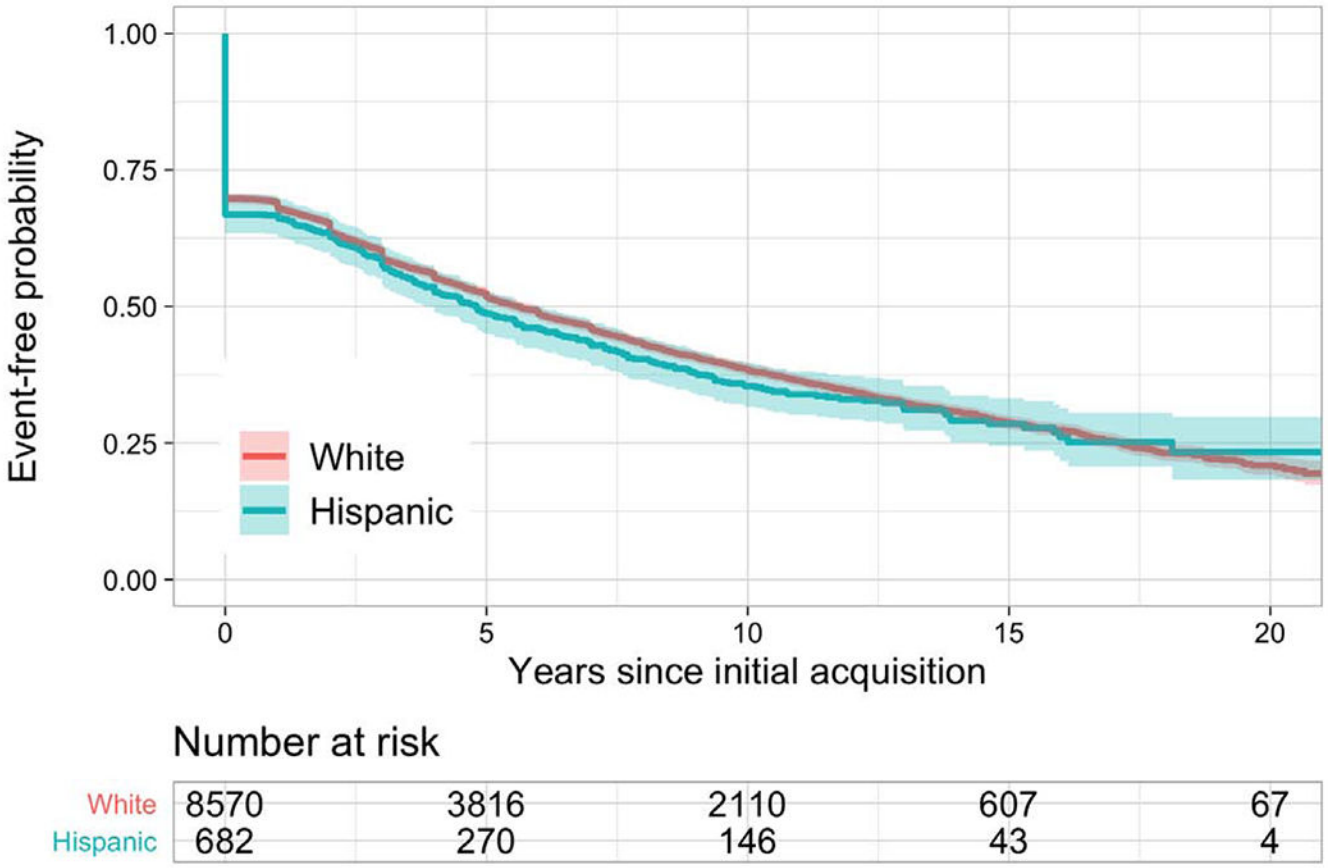

Figure 5: Kaplan-Meier Curves for the Risk of Conversion from Intermittent to Chronic Pseudomonas By Ethnicity

Hispanic patients had a shorter median duration of intermittent *P. aeruginosa* than white patients (4.8 years vs. 5.6 years) and were at 1.34 times higher risk for converting from intermittent to chronic *P. aeruginosa* (95% CI 1.20-1.49, p<0.001), adjusted for sex, CF-related diabetes, pancreatic insufficiency, CFTR mutation class, age of entry into CF Foundation Patient Registry, US Census Region, year of birth, number of cultures, and underweight.

Table 1:

Description of Characteristics By Ethnicity.

	Hispanic (n=788)	Non-Hispanic White (n=9676)	p-value
Sex, female (% female)	372 (47.2%)	4511 (46.6%)	0.8
Pancreatic Insufficiency (%)	749 (95.1%)	9376 (96.9%)	0.007
CFTR Mutation Class (%)			<0.001
Class I-III	473 (60.0%)	7779 (80.4%)	
Class IV-V	80 (10.2%)	611 (6.3%)	
Unknown	235 (29.8%)	1286 (13.3%)	
Enrollment Age, years median (range)	0.74 (0-21.6)	0.89 (0-22.0)	<0.001
CF-Related Diabetes (%)	242 (30.7%)	2968 (30.7%)	1.0
U.S. Census Region (%)			<0.001
Northeast	136 (17.3%)	2368 (24.5%)	
South	249 (31.6%)	2513 (26.0%)	
Midwest	76 (9.6%)	3077 (31.8%)	
West	326 (41.4%)	1682 (17.4%)	
Underweight (%)	447 (56.7%)	5647 (58.4%)	0.4
Maternal Education (%)			<0.001
College or more	379 (48.1%)	6279 (64.9%)	
High School or less	292 (37.1%)	1932 (20.0%)	
Missing	117 (14.8%)	1465 (15.1%)	
Paternal Education (%)			<0.001
College or more	212 (26.9%)	4416 (45.6%)	
High School or less	440 (55.8%)	3711 (38.4%)	
Missing	136 (17.3%)	1549 (16.0%)	
Annual Income			<0.001
<$50,000	237 (30.1%)	2507 (25.9%)	
$50,000-$90,000	74 (9.4%)	1511 (15.6%)	
>$90,000	67 (8.5%)	1877 (19.4%)	
Missing	410 (52.0%)	3781 (39.1%)	
Insurance			<0.001
Public	468 (59.4%)	3950 (40.8%)	
Private	310 (39.3%)	5637 (58.3%)	
None	10 (1.3%)	88 (0.9%)	
Missing	0	1 (0%)	

Table 2:

Probability of Pseudomonas Free at 2.5 and 5 years old

	Non-Hispanic White	Hispanic	p-value
2.5 years old			
Any Pseudomonas	78.2% (77.4-79.0%)	70.3% (67.2-73.6%)	<0.001
Mucoid Pseudomonas	98.4% (98.2-98.4%)	96.6% (95.3-97.9%)	<0.001
Chronic Pseudomonas	94.5% (94.0-94.9%)	90.1% (88.0-92.2%)	<0.001
MDR Pseudomonas	99.8% (99.7-99.9%)	99.4% (98.8-99.9%)	0.1
5.0 years old			
Any Pseudomonas	62.6% (61.6-63.5%)	53.2% (49.8-56.8%)	<0.001
Mucoid Pseudomonas	94.9% (94.4-95.3%)	88.2% (86.0-90.5%)	<0.001
Chronic Pseudomonas	88.9% (88.3-89.6%)	82.1% (79.5-84.8%)	<0.001
MDR Pseudomonas	99.5% (99.4-99.7%)	98.4% (97.5-99.2%)	<0.001

P-value is based on Ward-type test at the specific time period 2.5 and 5 years old.

Table 3:

Risk of Pseudomonas aeruginosa Acquisition in Hispanic Patients Compared to Non-Hispanic White Patients With and Without Inclusion of Socioeconomic Status Measures

	Full Models HR (95% CI)	Including Socioeconomic Status Measures HR (95% CI)
Any Pseudomonas	1.26 (1.16-1.38) p<0.001	1.24 (1.13-1.35) p<0.001
Mucoid Pseudomonas	1.59 (1.43-1.77) p<0.001	1.55 (1.39-1.73) p<0.001
Chronic Pseudomonas	1.39 (1.25-1.55) p<0.001	1.37 (1.23-1.52) P<0.001
MDR Pseudomonas	1.91 (1.64-2.23) p<0.001	1.85 (1.58-2.16) p<0.001
Conversion from Intermittent Pseudomonas	1.34 (1.20-1.49) P<0.001	1.31 (1.18-1.46) P<0.001

All Cox proportional hazard models were adjusted for sex, CF-related diabetes, pancreatic insufficiency, CFTR mutation class severity, age of entry into CF Foundation Patient Registry, year of birth, US Census Region, number of cultures, and underweight. Insurance status, maternal education, paternal education, and income was added to the full models as measures of socioeconomic status. Pancreatic insufficiency, CF-related diabetes, underweight, number of cultures, insurance status and income were entered as time-dependent.