

Early Diagnosis of Cystic Fibrosis in the Newborn Period and Risk of *Pseudomonas aeruginosa* Acquisition in the First 10 Years of Life: A Registry-Based Longitudinal Study

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ABSTRACT. *Objective.* Controlled clinical trial data have suggested that identifying asymptomatic cystic fibrosis (CF) patients through newborn screening improves health outcomes of affected children in the first decade of life. However, it is unclear whether these improvements also include a reduction in risk for bronchial infection, the major determinant of CF morbidity. The authors therefore investigated the association between early CF diagnosis and acquisition of *Pseudomonas aeruginosa*, the major bronchial pathogen, in the first decade of life.

Methodology. Longitudinal data on 3625 CF patients diagnosed between 1982 and 1990 and before 36 months of age were ascertained from the National Cystic Fibrosis Patient Registry. We compared *P aeruginosa* acquisition in the first 10 years of life among 4 groups: EAD (early asymptomatic diagnosis)—<6 weeks, by pre/neonatal screening, genotype, family history ($n = 157$); ESD (early symptomatic diagnosis) ($n = 227$); LAD (late asymptomatic diagnosis)—6 weeks to 36 months ($n = 161$); and LSD (late symptomatic diagnosis) ($n = 3080$). *P aeruginosa* acquisition was determined from yearly sputum and/or bronchoscopy cultures. Children whose CF diagnoses followed meconium ileus or whose cultures were obtained only from nasal samples were excluded from the study.

Results. Kaplan Meier analyses for *P aeruginosa* acquisition were conducted for each diagnostic group. Regression models were used to generate adjusted relative hazards with EAD as the referent group. Relative hazards were 0.9 (95% confidence interval [CI]: 0.7–1.2) for ESD, 0.8 (95% CI: 0.6–1.2) for LAD, and 1.0 (95% CI: 0.7–1.2) for LSD. The risk of acquiring *P aeruginosa* was therefore not significantly different between children diagnosed early, late, asymptotically, or symptomatically.

Conclusions. These data suggest that, despite improvements in other health outcomes from newborn screening for CF, early asymptomatic diagnosis of CF

does not affect *P aeruginosa* acquisition. *Pediatrics* 2001; 107:274–279; *cystic fibrosis, Pseudomonas aeruginosa, neonatal screening, Kaplan Meier, epidemiology*

ABBREVIATIONS. CF, cystic fibrosis; CFF, Cystic Fibrosis Foundation; EAD, early asymptomatic diagnosis; ESD, early symptomatic diagnosis; LAD, late asymptomatic diagnosis; LSD, late symptomatic diagnosis; CI, confidence interval; OR, odds ratio.

Cystic fibrosis (CF) is a common, serious genetic disorder affecting an estimated 30 000 individuals in the United States. The mean age at diagnosis of CF is 6 months. Most of the 1000 CF cases diagnosed annually in the United States are diagnosed by the time the patient is 3 years old.¹ The major cause of morbidity and mortality in CF patients is from respiratory infections, which lead to a subsequent decline in pulmonary function. Although antibiotics may be given as prophylaxis, they are more often administered orally or intravenously to control acute episodes of infection.

By the end of the first decade of life, *Pseudomonas aeruginosa* is the predominant bacterial pathogen colonizing the lower respiratory tract in CF patients.^{2,3,4} Although it is not the first pathogen to colonize the lungs of CF patients,⁵ it is the major pathogen contributing to pulmonary disease and decline in pulmonary function.^{6–11} Studies have demonstrated significant associations between *P aeruginosa* colonization and impaired pulmonary function, pulmonary deterioration, and mortality in CF patients.^{12,13} Once acquired, *P aeruginosa* is difficult to eradicate,¹⁴ often persisting until pulmonary failure and death.^{5,6,8,11}

Respiratory failure in CF patients is a consequence of lung damage resulting from intense inflammatory responses.^{3,10,11,15} Therefore, although *P aeruginosa* colonization is regarded as a leading contributor to death in CF patients in combination with lung inflammation and lung obstruction,^{6,16} it is the resulting pulmonary insufficiency and respiratory failure that ultimately lead to morbidity and mortality in CF patients.^{5,8}

A recent clinical trial in Wisconsin demonstrated improvements in nutritional status, measured by height and weight, in children identified with CF through newborn screening, compared with children identified by standard means (usually with the onset of symptoms).^{17–19} These findings suggested that

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newborn screening may lead to improved long-term health outcomes in children with CF. Better nutrition made possible by early diagnosis and treatment might also enable children with CF to delay acquisition of *P aeruginosa*, and remain free from infection with this ubiquitous organism as persons without CF are able to do. However, the same trial recently tested the hypothesis that *P aeruginosa* would be accelerated with early diagnosis attributable to increased interaction with older CF patients and increased exposure.¹⁴ The trial did not find that early diagnosis led to a delay or acceleration in *P aeruginosa* acquisition,^{14,19} but because of its limited sample size, it may not have had the power to detect a statistical difference. As *P aeruginosa* pathogenesis causes substantial morbidity and mortality in CF patients, any effect on *P aeruginosa* acquisition in children with CF would be significant.

Using data from CF patients in the national Cystic Fibrosis Foundation Patient Registry, we attempted to determine whether early asymptomatic diagnosis of CF is associated with acquisition of *P aeruginosa* in the first 10 years of life. The purpose of newborn screening is not only to identify newborns with CF, but also to diagnose CF before clinical symptoms present. In this study, early asymptomatic diagnosis (diagnosis before 6 weeks of age) is used to approximate a diagnosis from newborn screening.

METHODS

Study Population

The study population for this longitudinal study included approximately 4000 children with CF who were diagnosed between 1982 and 1990, registered in the Cystic Fibrosis Foundation (CFF) Patient Registry, and seen at 1 of the 111 accredited CF care centers in the United States and followed for up to 10 years. The CFF supports and accredits CF care centers nationwide. These centers provide a national network of specialized care for persons with CF and offer comprehensive diagnosis and treatment, as well as participation in clinical trials of experimental therapies. The CFF has sponsored the patient registry since 1966,²¹ requiring all CFF-accredited care centers to complete standardized questionnaires for all patients seen in their centers.²¹ The 1998 Annual Report of the CFF National Patient Registry reported 21 044 individuals with CF enrolled in the registry or approximately 91% of the estimated 23 000 CF patients under care in the United States.¹ Our analysis included children diagnosed with CF within 36 months of age. Only children with annual *P aeruginosa* cultures obtained by bronchoscopy or from sputum samples were included. Children who presented with meconium ileus, or whose *P aeruginosa* cultures were obtained only from nasal samples, were excluded.

CF Diagnosis

Diagnosis with CF was confirmed at CF care centers by sweat test, or by DNA analysis. We grouped children into 4 categories: early asymptomatic diagnosis (EAD), early symptomatic diagnosis (ESD), late asymptomatic diagnosis (LAD) and late symptomatic diagnosis (LSD). Early diagnosis was defined as diagnosis before 6 weeks of age, and late diagnosis was defined as diagnosis between 6 weeks and 36 months of age. We selected 6 weeks as the threshold for early diagnosis because it is considered standard for newborn screening programs. Asymptomatic diagnosis is defined as diagnosis by family history, genotype, prenatal diagnosis (chorionic villus sampling, amniocentesis), or neonatal screening. Symptomatic diagnosis is defined as diagnosis because of clinical presentation with acute or persistent respiratory symptoms, failure to thrive or malnutrition, steatorrhea, abnormal stools, malabsorption, electrolyte imbalance, nasal polyps or sinus disease, rectal prolapse, or liver disease. In addition to diagnostic information, the National CF Patient Registry includes demographic,

health care indicators, microbiology, lung function, anthropometric, and health status information. Methods for collection of this data are described elsewhere.²¹ Characteristics specifically of interest for this study included *P aeruginosa* cultures, method of diagnosis, age at diagnosis, race, gender, acute exacerbation, pancreatic status, year of birth, and state of birth.

Statistical Methods

Univariate and stratified analyses were conducted for the cohort at baseline, which was defined as a CF patient's first visit to a CF care center. Statistical significance was set at $P < .05$, two-sided. All analyses were performed with SAS 6.12 for Windows (SAS Institute, Cary, NC). There was sufficient power (>80%) to detect decreases or increases in risk for *P aeruginosa* acquisition of at least 0.8 or 1.2.

Colonization rates for *P aeruginosa* by diagnostic category (EAD, ESD, LAD, LSD) were assessed longitudinally, from time of diagnosis with CF to 10 years of age. Colonization of *P aeruginosa* was defined by a positive culture from sputum or bronchoscopy. It should be noted that between 1982 and 1990, only 85 cultures by bronchoscopy were obtained to identify *P aeruginosa* acquisition; the remainder and therefore vast majority of cultures included in this study to measure colonization and acquisition were ascertained from sputum. The proportion of patients colonized with *P aeruginosa* was calculated by age; crude and adjusted odds ratios (ORs) were calculated at baseline and at 1, 6, and 10 years of age. Adjusted ORs were calculated by multivariate logistic regression, adjusting for race, gender, acute exacerbation, pancreatic insufficiency, year of birth, and state of birth (dichotomized into states universally screening for CF and states who are not). All covariates were dichotomized in the model except year of birth, which was categorized into tertiles (1979–1984, 1985–1987, 1988–1990). Year of birth was originally divided into quartiles as seen in Table 1; however, because of the small number of individuals born between 1979 and 1981, they were combined with individuals born between 1982 and 1984. Acute exacerbation was defined as hospitalization or home-based course of intravenous antibiotic therapy for respiratory illness. Adjusted ORs with 95% confidence intervals (CIs) for *P aeruginosa* colonization are reported for 1, 6, and 10 years of age.

The data were also analyzed with Kaplan Meier and Cox proportional hazards regression models, with age as the time scale and time to *P aeruginosa* acquisition (in years) as the outcome. *P aeruginosa* acquisition for each CF patient was defined as the first documented positive culture of *P aeruginosa* by sputum or bronchoscopy. Relative hazards were adjusted for race, gender, acute exacerbation, pancreatic status, year of birth, and state of birth. All covariates were categorized as in the logistic regression models. Adjusted relative hazards with 95% CIs for *P aeruginosa* acquisition are reported.

RESULTS

Table 1 displays demographic and clinical characteristics of all children included in the study at their baseline visit. The median ages of diagnoses were 3.6 weeks for EAD, 4.2 weeks for ESD, 2.8 months for LAD, and 6 months for LSD. There were no significant differences among the 4 diagnostic groups in gender, ethnicity, or $\Delta F508$ mutation status. However, there were significant differences among the groups in race, pancreatic status, height and weight, year of birth, *P aeruginosa* colonization, and state of birth (Table 1). Despite significant differences in height and weight among the 4 diagnostic groups at baseline, they were not associated with *P aeruginosa* acquisition and their inclusion of height and weight in multivariate models did not affect the results; they were therefore not included in the final multivariate model.

Logistic regression models were used to determine significant differences in colonization with *P aeruginosa* between the 4 diagnostic groups while con-

TABLE 1. Demographic Characteristics of CF Patients ($n = 3625$) From the CFF Patient Registry At Time of Diagnosis (1982–1990), Excluding Those Diagnosed >3 Years of Age or With Meconium Ileus*

Characteristic	EAD ($n = 157$)	ESD ($n = 227$)	LAD ($n = 161$)	LSD ($n = 3080$)	P value
Age					
Median	3.6 wks	4.2 wks	11.4 wks (2.8 mo)	25 wks (6 mo)	.001
Range	birth to <6 wks	birth to <6 wks	6 wks–36 mo	6 wks–36 mo	
Gender					
Male	78 (50%)	130 (57%)	80 (50%)	1639 (53%)	.379
Female	79 (50%)	97 (43%)	81 (50%)	1441 (47%)	
Race					
White	156 (99%)	223 (98%)	160 (99%)	2931 (95%)	.012
Black	1 (1%)	4 (2%)	1 (1%)	128 (4%)	
Other				20 (1%)	
Ethnicity					
Non-Hispanic	147 (95%)	213 (97%)	152 (96%)	2860 (95%)	.591
Hispanic	8 (5%)	6 (3%)	6 (4%)	136 (5%)	
Δ F508 status					
F508/F508	56 (58%)	55 (50%)	49 (54%)	751 (54%)	.562
F508/other	12 (13%)	23 (21%)	16 (18%)	216 (16%)	
F508/unknown	21 (22%)	17 (16%)	19 (21%)	264 (19%)	
Other	7 (7%)	14 (13%)	6 (7%)	153 (11%)	
Pancreatic status					
Insufficient	12 (86%)	15 (100%)	16 (89%)	311 (96%)	.022
Sufficient	2 (14%)		2 (11%)	14 (4%)	
NCHS height					
$\leq 5^{\text{th}}$ percentile	14 (10%)	49 (24%)	25 (17%)	1208 (42%)	.001
$>5^{\text{th}}$ percentile	126 (90%)	157 (76%)	120 (83%)	1642 (58%)	
NCHS weight					
$\leq 5^{\text{th}}$ percentile	27 (18%)	59 (27%)	32 (21%)	1421 (48%)	.001
$>5^{\text{th}}$ percentile	120 (82%)	160 (73%)	123 (79%)	1543 (52%)	
<i>P. aeruginosa</i>					
cultured positive	3 (4%)	13 (12%)	7 (9%)	288 (20%)	.001
cultured negative	75 (96%)	92 (88%)	74 (91%)	1169 (80%)	
Birth year					
1979–1981	2 (1%)	1 (1%)	10 (6%)	273 (9%)	.001
1982–1984	48 (31%)	75 (33%)	53 (33%)	1007 (33%)	
1985–1987	66 (42%)	82 (36%)	54 (34%)	1083 (35%)	
1988–1990	41 (26%)	69 (30%)	44 (27%)	717 (23%)	
State of birth					
WI, CO, WY	55 (35%)	10 (4%)	35 (22%)	91 (3%)	.001
All others	101 (65%)	217 (96%)	125 (78%)	2975 (97%)	

* Because of missing data, numbers reported by characteristic may not add up to total number of individuals for each diagnostic group.

trolling for confounders. Logistic regression models controlling for race, gender, acute exacerbation, pancreatic status, year of birth, and state of birth demonstrated no differences between the 4 diagnostic groups with regards to *P. aeruginosa* colonization at 1, 6, or 10 years of age (Table 2). Individuals with at least 1 reported acute exacerbation were consistently more likely to be colonized with *P. aeruginosa*.

To assess whether early diagnosis was associated with the acquisition of *P. aeruginosa*, we performed a Kaplan Meier analysis for *P. aeruginosa* acquisition (defined as the first visit in which a culture is positive for *P. aeruginosa*) for the 4 diagnostic categories by age (Fig 1). A Cox proportional hazard model adjusting for race, gender, acute exacerbation, pancreatic status, year of birth, and state of birth did not yield significant differences between relative hazards for *P. aeruginosa* acquisition in ESD, LAD, or LSD groups compared with the EAD group (Table 3). Significantly increased risk of *P. aeruginosa* acquisition was associated with at least 1 acute exacerbation (OR 1.6; 95% CI: 1.5–1.8), being born in a later cohort (1988 and beyond) (OR 1.4; 95% CI: 1.3–1.4), and being born in a state not universally screening for CF (OR 1.5; 95% CI: 1.2–1.9).

TABLE 2. Final Logistic Regression Model for *P. aeruginosa* Colonization in CF Patients, Measured via Bronchoscopy and Sputum, at Ages 1, 6, and 10 Years, by Diagnosis (Excluding Patients With Meconium Ileus or Diagnosed >3 Years of Age)

Variable	1 Year OR (95% CI)	6 Year OR (95% CI)	10 Year OR (95% CI)
ESD*	1.3 (0.5, 3.3)	0.9 (0.4, 1.9)	1.2 (0.6, 2.5)
LAD*	1.1 (0.4, 3.1)	2.1 (0.9, 5.3)	1.0 (0.5, 2.3)
LSD*	1.0 (0.5, 1.9)	1.2 (0.7, 2.3)	1.0 (0.6, 1.6)
Race (referent: white)	1.7 (0.8, 3.8)	1.0 (0.5, 1.9)	1.4 (0.7, 2.8)
Gender (referent: male)	1.2 (0.9, 1.7)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)
Acute exacerbation	1.8 (1.3, 2.5)	3.0 (2.2, 4.0)	1.8 (1.4, 2.3)
Pancreatic status**	—	1.7 (0.9, 3.3)	2.6 (1.3, 5.5)
Year of birth***	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.9, 1.3)
State of birth (referent: WI, CO, WY)	2.4 (0.9, 6.5)	2.0 (1.0, 4.0)	1.3 (0.7, 2.4)

* ESD, early symptomatic diagnosis; LAD, late asymptomatic diagnosis; LSD, late symptomatic diagnosis; EAD, early asymptomatic diagnosis (referent).

** Pancreatic status was not assessed in children at 1 year of age and therefore not included in the logistic regression model for 1 year of age.

*** Year of birth categorized into 3 groups: 1979–1984, 1985–1987, and 1988–1990; the number of individuals in the 1979–1981 quartile was too small for analysis by quartiles.

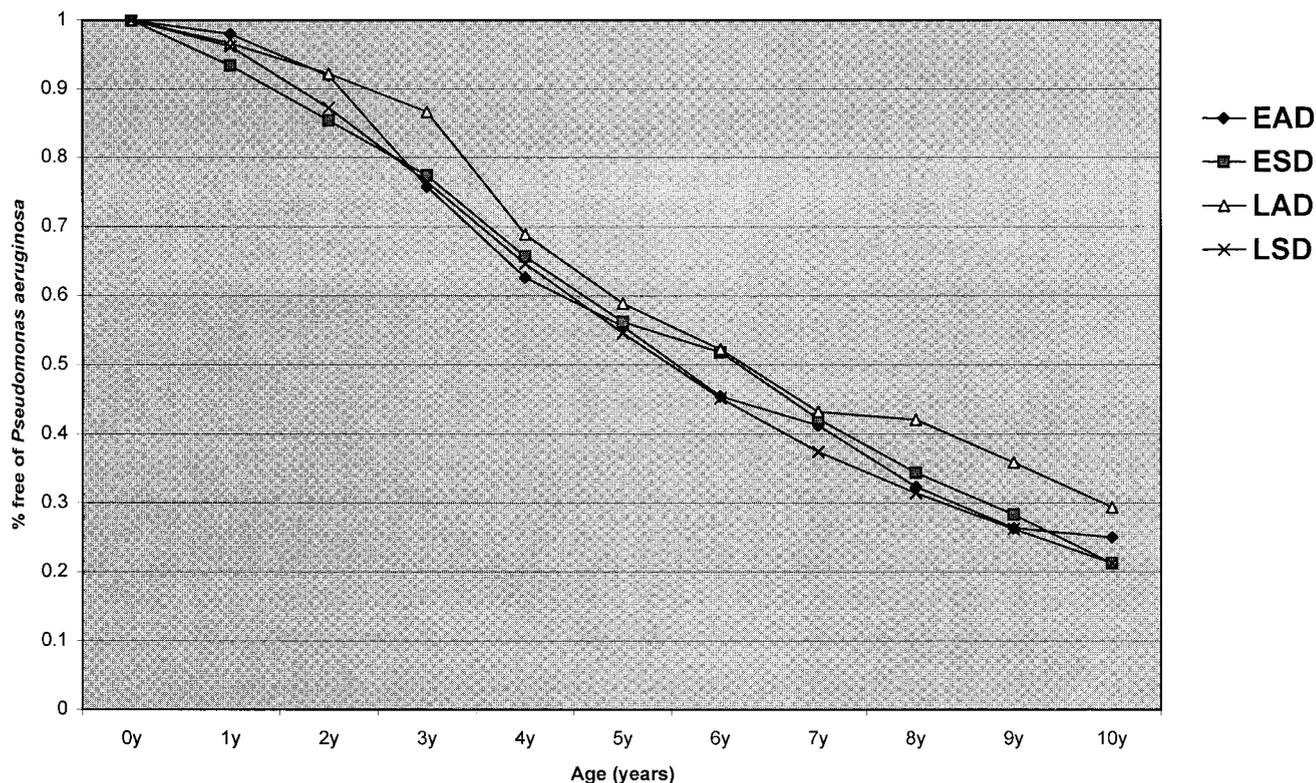


Fig 1. Kaplan Meier analysis of *Pseudomonas* acquisition in CF patients measured through sputum and/or bronchoscopy, from ages 1 through 10 years, by diagnosis (excluding patients with meconium ileus).

TABLE 3. Final Cox Proportional Hazards Model for *P aeruginosa* Acquisition in CF Patients, Measured via Bronchoscopy and Sputum, by Diagnosis (Excluding Patients With Meconium Ileus or Diagnosed >3 Years of Age)

Variables	Relative Hazards (95% CI)
ESD*	0.9 (0.7, 1.2)
LAD*	0.8 (0.6, 1.2)
LSD*	1.0 (0.7, 1.2)
Race (referent: white)	1.0 (0.8, 1.3)
Gender (referent: male)	1.1 (1.0, 1.2)
Acute exacerbation	1.6 (1.5, 1.8)
Pancreatic status	1.4 (1.0, 2.0)
Year of birth	1.4 (1.3, 1.4)
State of birth (referent: WI, CO, WY)	1.5 (1.2, 1.9)

* ESD indicates early symptomatic diagnosis; LAD, late asymptomatic diagnosis; LSD, late symptomatic diagnosis; EAD, early asymptomatic diagnosis (referent).

** Year of birth categorized into 3 groups: 1979–1984, 1985–1987, and 1988–1990. The number of individuals in the 1979–1981 quartile was too small for analysis by quartiles.

DISCUSSION

As *P aeruginosa* is the major organism contributing to respiratory tract infection and associated morbidity and mortality in persons with CF, the goal of this study was to determine whether early diagnosis of CF by newborn screening delays *P aeruginosa* acquisition, or accelerates acquisition because of increased interaction with older CF children. This observational study of patients from the CFF Patient Registry did not find significant differences between the 4

diagnostic groups (EAD, ESD, LAD, and LSD) in *P aeruginosa* acquisition.

Use of the CFF Patient Registry provided many benefits to this study. This large registry offered sufficient sample size and power to examine whether *P aeruginosa* acquisition was delayed in children who were diagnosed with CF asymptotically and before 6 weeks of age. Despite the exclusion criteria imposed, over 3600 patients were included in the analyses. Furthermore, longitudinal analysis was possible to assess *P aeruginosa* acquisition with adjustment for possible confounding factors. All multivariate analyses were adjusted for year of birth because of concern that improving treatments over time could lead to a cohort effect. State of birth was also adjusted for in the multivariate analysis, dichotomizing between states with newborn screening programs for CF (Wisconsin, Wyoming, Colorado) and the remaining states to control for any differences in treatments in the newborn populations in these states. It is possible that children diagnosed in states with newborn screening programs for CF may have had differences in treatment, possibly affecting *P aeruginosa* acquisition or colonization, which is the outcome of interest.

This study found that children who were born more recently in a state without newborn screening for CF and who had at least 1 acute exacerbation were at significantly increased risk for *P aeruginosa* acquisition. The association between recent births and *P aeruginosa* acquisition may be attributable to

the increasing ability of the clinics to obtain cultures from newborns who normally do not have the ability to produce sputum for culture. The association between children from states without universal screening for CF and *P aeruginosa* acquisition is unclear because universal screening was initiated midway through the inclusion period (1982 to 1990). The association between pancreatic status (insufficiency) and *P aeruginosa* acquisition is plausible and may be serving as a proxy for $\Delta F508$ mutational status, which has been demonstrated to be involved in bacterial colonization. Lastly, the association between acute exacerbation and *P aeruginosa* is also a plausible one. Children reporting >1 acute exacerbations at the time of their annual examinations are not only more susceptible to infection because of their respiratory complications, but they may also have increased exposure to organisms from their hospitalization, leading to subsequent detection of colonization at their next CF clinic visit. However, it is unclear whether acute exacerbations preceded *P aeruginosa* colonization or whether colonization led to the documented hospitalization or home-based course of intravenous antibiotic therapy for respiratory illness.

There are several issues that must be considered when interpreting these findings. First, this was an observational study and there were unmeasured factors that cannot be controlled for as they might be in a controlled clinical trial such as access to care. Other biases include possible selection bias; for example, although the registry includes most CF patients under care in the United States, those who are not enrolled in the clinics may be older in age and healthier in general.²¹ Excluding persons who remain asymptomatic for >3 years may also have biased our analysis to include a sicker cohort. Nevertheless, it is important to note these biases would be minimal because the majority of CF patients are diagnosed by 3 years of age. In clinical practice, the healthiest nonsputum-producing patients may be less likely to have cultures, again biasing the cohort to sicker patients and higher *P aeruginosa* rates. This bias would apply to the entire cohort, equally to each diagnostic category; however, the sicker referent group would make differences between the groups more difficult to identify.²¹

There is no standard method for detecting *P aeruginosa* in lower airways in this registry; although potential for misclassification was reduced by excluding cultures from nasal samples. The majority of cultures were obtained from sputum with a minimal number of cultures obtained by bronchoscopy. Methods for ascertaining culture were limited to culture obtained by sputum, from throat/nasal swab, or by bronchoscopy. Therefore, for this study, culture from sputum was the best available method for identifying lower respiratory infection. Furthermore, not every patient was cultured for *P aeruginosa* in any given year. Therefore, logistic regression models at specific age groups do not include all eligible children in the population. Estimates of risk calculated longitudinally are therefore more reliable than estimates from

cross-sectional data, as all children were included for this analysis. In this analysis, *P aeruginosa* acquisition was defined as the first positive culture documented in the registry. As cultures were not necessarily attained every year, there is potential for delayed identification of acquisition, possibly resulting in a more conservative estimate of risk for the overall time period.

The Wisconsin clinical trial compared *P aeruginosa* acquisition of patients diagnosed through neonatal screening and treated in early infancy with those identified by standard diagnostic methods. Although they found no differences in acquisition between the diagnostic categories, there were differences when stratified by the type of CF care center. A significant difference was observed with earlier acquisition of *P aeruginosa* in an urban CF care center where there was more opportunity for social interactions between younger CF patients and older CF patients.¹⁴ Subsequent analyses further identified the use of aerosols (aerosolized saline, bronchodilators, antibiotics, or DNase) to be the significant risk factor for *P aeruginosa* acquisition.²²

Despite the limitations discussed, the CFF Patient Registry cohort offers unique opportunities to longitudinally investigate *P aeruginosa* acquisition in CF patients. The results presented in this study are consistent with those observed in the Wisconsin Clinical Trial, where acquisition for *P aeruginosa* was not associated with early diagnosis of CF. Policy decisions regarding newborn screening for CF should include *P aeruginosa* acquisition among the health outcomes to be considered.

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TEACHING HOSPITALS TOO BUSY FOR CURIOSITY

“... He needs someone who can spend time with him. Get a new history, read the chart, ask questions. You and I don’t have the time. He needs someone who’s going to make him his or her project.”

I nodded, and then we got on with our work. I was caring for about 15 patients at the time. He, in addition to his teaching and research responsibilities, was seeing patients in the clinic. There didn’t seem to be any time to grapple with a medical mystery. We both realized we were failing our patient by not devoting adequate time to his problem, but we were too busy to care enough to do something about it.

This case is emblematic of the environment in teaching hospitals today. Such institutions were once places that stoked intellectual curiosity, but this virtue is fast succumbing to the pressures of cost-cutting and 10-minute patient visits that affect the rest of medicine.

Resident and attending physicians today are running on a treadmill that is moving faster and faster. Residents are caring for more and sicker patients, and dealing with quicker patient turnover. This is driven partly by medical advances—only very sick AIDS patients now require hospitalization, for example—but mainly by the financial bottom line.

Teaching hospitals have turned teaching into a business in order to survive. . .

One of the casualties of this new environment has been largely neglected: curiosity. Residents today are preoccupied with getting their work done. Anything that gets in the way—even a bona fide medical mystery—is more often seen as a bother rather than a learning opportunity.

Jauhar S. *New York Times*. September 6, 2000

Noted by JFL, MD