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LONGITUDINAL DEVELOPMENT OF INITIAL, CHRONIC AND MUCOID *PSEUDOMONAS AERUGINOSA* INFECTION IN YOUNG CHILDREN WITH CYSTIC FIBROSIS

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Abstract

Background—While the emergence of chronic and mucoid *Pseudomonas aeruginosa* (*Pa*) infection are both associated with poorer outcomes among CF patients, their relationship is poorly understood. We examined the longitudinal relationship of incident, chronic and mucoid *Pa* in a contemporary, young CF cohort in the current era of *Pa* eradication therapy.

Methods—This retrospective cohort was comprised of patients in the U.S. CF Foundation Patient Registry born 2006–2015, diagnosed before age 2, and with at least 3 respiratory cultures annually. Incidence and age-specific prevalence of *Pa* infection stages (initial and chronic [≥ 3 *Pa*+ cultures in prior year]) and of mucoid *Pa* were summarized. Transition times and the interaction between *Pa* stage and acquisition of mucoid *Pa* were examined via Cox models.

Results—Among the 5,592 CF patients in the cohort followed to a mean age of 5.5 years, 64% (n=3,580) acquired *Pa*. Of those, 13% (n=455) developed chronic *Pa* and 17% (n=594) cultured mucoid *Pa*. Among those with mucoid *Pa*, 36% (211/594) had it on their first recorded *Pa*+ culture, while mucoid *Pa* emerged at or after entering the chronic stage in 12% (73/594). Mucoidy was associated with significantly increased risk of transition to chronic *Pa* infection (HR=2.59, 95% CI 2.11, 3.19).

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Conclusions—Two-thirds of early-diagnosed young children with CF acquired *Pa* during a median 5.6 years of follow up, among whom 13% developed chronic *Pa* and 17% acquired mucoid *Pa*. Contrary to our hypothesis, 87% of young children who developed mucoid *Pa* did so before becoming chronically infected.

Keywords

Pseudomonas aeruginosa; mucoidy; pediatric; cystic fibrosis; epidemiology

INTRODUCTION

While survival continues to improve in cystic fibrosis (CF), the major cause of morbidity and mortality remains progressive lung disease due to chronic endobronchial bacterial infection, inflammation and structural airway damage. *Pseudomonas aeruginosa* (*Pa*) is the sentinel respiratory pathogen in CF; by adulthood 70% of CF patients are infected (1), and *Pa* infection has been linked to poorer outcomes and greater mortality (2, 3). The progression of *Pa* infection is frequently characterized in stages: initial to intermittent to chronic (4). While initial *Pa* infection has no clear effect on clinical outcomes (5), chronic infection has been associated with lower lung function, greater structural damage on chest imaging and poorer nutritional status (6–8). *Pa* infection in the CF lung can also be characterized by phenotypic changes, the best-known being mucoidy. Like chronic infection, mucoidy has clearly been associated with worse clinical outcomes (9–11). While the accepted belief is that chronic *Pa* infection precedes mucoid infection (12, 13), in fact, the longitudinal relationship between the emergence of chronic *Pa* infection and of mucoidy has only been minimally evaluated (14), and recent studies suggest that this paradigm might be overly simplistic (15–17).

Among infants born between 1985 and 1994 enrolled in the Wisconsin Neonatal Screening Project, more than 80% had acquired *Pa* by age 4 (10). Since that study (and in part based on its findings), aggressive antibiotic treatment of initial *Pa* infection to delay or prevent chronic / mucoid infection has become standard of care in the U.S. (18–21). Recent U.S. nationwide data show reduced age-specific prevalence and incidence of *Pa* over the past decade compared to the decade prior (1), but trends in the prevalence of chronic *Pa* and mucoid *Pa* were not evaluated.

We utilized the CF Foundation Patient Registry (CFFPR) to describe stages of *Pa* infection and mucoid *Pa* in a young CF cohort in the current era of *Pa* eradication therapy. The objectives of this analysis were to (1) characterize the emergence and age-specific prevalence of *Pa*, chronic *Pa* and mucoid *Pa* in young CF patients and (2) examine the relationship between stages of *Pa* infection and mucoidy. We hypothesized that emergence of mucoid *Pa* would occur predominantly following the development of chronic infection among young people with CF.

METHODS

Study Design and Population

The CFFPR is a comprehensive repository of clinical and epidemiological data collected from CF patients across the United States since 1966 (22, 23). In 2003, data began to be collected at each clinic encounter (typically quarterly) rather than annually, and in 2006 information on chronic inhaled antibiotic use was added to the CFFPR (22). We therefore performed a retrospective, longitudinal cohort study using CFFPR data from 2006 to 2015. Because we aimed to characterize the transition from incident to chronic and mucoid Pa, we enrolled patients born on or after January 1, 2006 who were diagnosed and had first encounter data recorded in the CFFPR by age two. Because detection of *Pa*, mucoid *Pa*, and the definition of chronic *Pa* are all highly dependent on respiratory culture frequency, the cohort was further restricted to those with at least three quarters (3-month intervals) with respiratory cultures recorded per year for a minimum of two years, or if born in 2015, at least three quarters with cultures recorded that year (i.e., those who were generally following U.S. CF Foundation Care Guidelines calling for quarterly cultures (21).)

Data and variables

Respiratory culture data were evaluated by age quarter intervals (i.e., four quarters per each year of age). The presence of at least one *Pa*+ culture in a given age quarter defined that age quarter as positive for *Pa*. For each patient the age quarter of initial *Pa* was defined as the quarter of first lifetime isolation of *Pa* (i.e. incident *Pa*). Because left censoring can impact *Pa* incidence estimates, a sensitivity cohort was also analyzed excluding patients if their first recorded culture was positive for *Pa*. The age of first chronic infection was defined as the first age quarter in which at least three age quarters in the preceding year were *Pa*+ (e.g. 3/3, 3/4, or 4/4 cultures positive for *Pa* in the preceding year). Following first chronic infection, the subsequent year was assessed to determine reversion to *Pa* free (defined as zero *Pa*+ cultures in the year, with cultures recorded in at least one age quarter). The age quarter of first mucoid *Pa* recorded in the CFFPR was also calculated for each patient. The CFFPR does not record acute courses of inhaled or oral antibiotics, but recorded use of chronic inhaled antibiotics (tobramycin, aztreonam, or other) during the year a person became chronically infected with *Pa* was summarized. Demographic and diagnostic information included sex, race, ethnicity, diagnosis method and age, F508del mutation status and CF transmembrane conductance regulator (CFTR) functional class (24, 25).

Statistical Methods

Age-specific prevalence of *Pa* was calculated in each age category. Kaplan-Meier curves were generated age of initial, first mucoid, and first chronic *Pa*, and for transition times from initial to chronic and mucoid *Pa* infection, and Cox proportional hazards (PH) models were fit. All p-values are two-sided. See online Supplemental Material for details, sensitivity analyses and Kaplan-Meier curves comparing time to *Pa* acquisition by CFTR mutation functional class.

RESULTS

Demographics and Pa Prevalence & Incidence

Of the 7070 CF patients in the CFFPR born between 2006 and 2015, 5592 met inclusion criteria (Table 1). Sixty six percent were diagnosed through prenatal or newborn screening. Mean age at diagnosis was 1 month and mean age of first recorded respiratory culture in the CFFPR was 0.29 years (SD=0.22). Average follow-up time (from birth until last recorded culture) was 5.5 years (SD =2.5, median 5.6, range = 0.6, 9.9 years); 43% of the cohort had follow-up to at least 6 years of age and 19% were observed past age 8.

Over all the possible person-age quarters in the cohort, respiratory cultures were recorded in 82%. Cultures were predominantly from oropharyngeal swabs (84%), with sputum and bronchoalveolar lavage samples less common, 13% and 2% respectively. The prevalence of non-mucoid *Pa* by age was relatively constant across each age interval (0–9 years), ranging from 15 to 26% (Figure 1a), with slight decreases after 2 years of age. The prevalence of mucoid *Pa*, however, rose steadily with age, from 1% in the first year to approximately 8% at age 9 (Figure 2a). Similarly, the prevalence of chronic *Pa* rose steadily from <1% in the first year to 6.7% by age 9 (Figure 1b).

More than half of all patients (3580/5592=64%) became *Pa* positive during the observation period. Kaplan-Meier curves for time to initial *Pa*, first mucoid and first chronic *Pa* as well as transition times are shown in Figures 2a–e. The median age at initial *Pa* for all 5,592 patients was 2.6 years (95% CI =(2.4, 2.9), Figure 2a). Approximately one in ten patients developed mucoid *Pa* (594/5,592=10.6%), or 16.6% of the 3,580 *Pa*+ patients. Notably, 35.5% (211/594) of those with mucoid *Pa* acquired it at the time of first *Pa* positive culture. Among all patients, 8.1% (455/5,592) developed chronic *Pa*, or 12.7% of the *Pa*+ patients. In a sensitivity analysis excluding the 472 participants whose first recorded respiratory culture was *Pa*+, results were essentially unchanged (Supplemental Table 1). Among those meeting the definition for chronic *Pa*, 83% (n=376) reported inhaled antibiotic use in the concurrent year, with the vast majority being inhaled tobramycin (94.7% [356/376]); 17.3% (65/376) reported inhaled aztreonam and 2% other inhaled antibiotic use. In the year after meeting the chronic definition, 27% (124/455) reverted to *Pa* free.

Table 1 compares the characteristics of patients who remained *Pa* free versus those who acquired *Pa* (N=2,012 vs. 3,580), mucoid *Pa* (N=594) and chronic *Pa* (N=455). Compared to patients who remained *Pa* free, patients who acquired *Pa* were more likely to have two functional classes I to III CFTR mutations (76% vs. 64%), less likely to be diagnosed by newborn screening (58% vs. 67%), were followed for a longer duration (mean 6.0 vs. 4.6 years) and had more quarters with cultures recorded. Similarly, compared to patients who remained *Pa* free, those who developed mucoid *Pa* or chronic infection were more likely to be followed for a longer duration (mean=6.9–7.0 years) and were more likely to have two severe CFTR mutations (79–81%).

Temporal Relationships between Chronic and Mucoid Pa

Table 2 summarizes the multiple transition patterns observed between initial, chronic and mucoid *Pa* infection in our cohort. Given the young age of our cohort and relatively short

observation period, most patients who acquired *Pa* did not go on to develop chronic or mucoid *Pa* (column 1). Among those who did progress, progression to mucoid *Pa* only was the most common pattern (N=371; 10% of *Pa*+ patients), occurring more often than transition to chronic *Pa* only (N = 232, 6%). We hypothesized that young patients with CF would culture mucoid *Pa* after becoming chronically infected; however, only 10% of those who developed mucoid *Pa* did so after reaching the chronic *Pa* stage and another 2% had mucoid co-occur with chronic *Pa* infection (Table 2, last column). First mucoid *Pa* actually *preceded* chronic *Pa* infection in 87% of those with mucoid *Pa* (62% developed mucoid *Pa* only, while 25% developed mucoid *Pa* and then chronic *Pa*).

The risks of progressing to chronic *Pa* and mucoid *Pa* were inter-related (Supplemental Table 2). Entering the chronic *Pa* stage did not significantly increase the risk of developing mucoid *Pa* (hazard ratio (HR) = 0.99, 95% CI= 0.76, 1.28). However, acquiring mucoid *Pa* increased the risk of developing chronic *Pa* (HR=2.59; 95% CI=2.11, 3.19, $p<0.001$), adjusted CFTR mutation functional class, race, sex, diagnosis type, and number of respiratory cultures. In addition, high risk CFTR functional class (2 mutations in class I to III) was associated with earlier acquisition of initial *Pa*, chronic *Pa*, mucoid *Pa* and transition times from initial to both chronic and mucoid *Pa* compared to residual function (at least 1 class IV or V mutation) (Supplemental Figure 1a–e).

DISCUSSION

In this analysis, we characterized the emergence of chronic *Pa* and mucoid *Pa* as two, often independent, stages of *Pa* infection clearly associated with poorer outcomes. We focused on young patients, to capture the progression from initial to chronic and mucoid *Pa*, and because the outcomes of chronic or mucoid *Pa* might be easier to alter with aggressive treatment in young children than in older patients with more established *Pa* infection.

In our large, contemporary U.S. cohort of children diagnosed with CF before age 2 and followed for a median of 6 years, nearly two-thirds acquired *Pa*. In contrast to studies conducted prior to widespread use of *Pa* eradication regimens (10), age-specific prevalence of non-mucoid *Pa* from birth to age 9 ranged from 26 to 15%. Progression to chronic *Pa* and mucoid *Pa* occurred in a substantial minority of those who acquired *Pa* (13% and 17%, respectively). In addition, the prevalence of both chronic and mucoid *Pa* rose with age, increasing from <1% in the first year of life to 7% at age 9 for chronic *Pa* and 8% for mucoid *Pa*.

Prior publications evaluating the emergence or prevalence of chronic *Pa* in CF have primarily focused on older patients (4, 6, 7, 26). More recently, in the EPIC trial of standardized *Pa* eradication regimens for newly acquired Pa (mean age 7.6 years) (27), chronic *Pa* developed in 23% of those who achieved sustained eradication in the original trial and 56% of those who did not (median follow up of 5 years) (16). The proportions acquiring mucoid *Pa* were 17% and 33%, respectively. The lower prevalence of chronic and mucoid *Pa* in our study was likely explained by the younger age and shorter follow up of our cohort.

Mucoidy is a well-characterized adaptation of Pa to the CF airway, due to excessive production of extracellular polysaccharide alginate. The emergence of mucoid *Pa* has been clearly implicated in poorer clinical outcomes in CF patients (9–11). A widely held paradigm is that initial *Pa* progresses first to chronic and then to mucoid *Pa* (12, 13). However, our results and those of others (14, 15, 28) suggest that this paradigm may be overly simplistic. In the Australasian CF Bronchoalveolar Lavage (ACFBAL) randomized controlled trial of BAL-directed therapy in infants with CF, 7% of lower airway isolates were mucoid even though none of the children met the definition of chronic *Pa* infection (15). Similarly, in the Australian AREST CF study involving annual BAL in CF patients <6 years of age, 18% of initial lower airway *Pa* was mucoid (28). A recent evaluation of phenotypes of upper airway *Pa* isolates from children enrolled in the EPIC Observational Study identified mucoidy in 8% of cultures of newly detected *Pa* and found a significant relationship between mucoidy and risk of subsequent pulmonary exacerbation requiring IV antibiotics that was consistent across infection stage (14). Finally, a study of the phenotypic characteristics of incident *Pa* isolates in children with CF in Toronto showed mucoidy to be significantly associated with failure of *Pa* eradication regimens, occurring in 71% of those who failed to eradicate vs. 31% who achieved eradication (17).

In our cohort, we specifically examined the temporal relationships of initial, mucoid and chronic *Pa* and found multiple patterns of transition. Contrary to our hypothesis, among those developing mucoid *Pa*, it preceded chronic *Pa* in 87%; indeed, 36% had mucoid *Pa* at the time of first lifetime *Pa* (despite limiting our cohort to those with a respiratory culture recorded prior to age two), even when those whose first recorded culture was *Pa+* were excluded. Taken together, these studies clearly demonstrate that mucoidy can occur early in *Pa* infection and can adversely affect clinical outcomes, suggesting it could be an important indicator of disease progression risk even in young patients without chronic infection, and may increase the risk of chronic infection because of its difficulty to treat.

In the most extensive prior longitudinal evaluation of mucoidy in CF, 56 children in the Wisconsin Neonatal Screening Trial born between 1985 and 1994 (prior to routine *Pa* eradication regimens) were followed to age 16 (10). Non-mucoid and mucoid *Pa* were acquired at median ages of 1.0 and 13.0 years, respectively. The median transition time from non-mucoid to mucoid *Pa* was 10.9 years, and appeared to be extended by anti-*Pa* antibiotics. Transition to mucoid *Pa* correlated with deterioration in cough scores, chest radiograph scores and pulmonary function; in contrast, there was no correlation of acquisition of non-mucoid *Pa* with clinical deterioration. In our contemporary cohort, the median age at initial *Pa* was 1.4 years among those who acquired *Pa* and 2.6 years overall, similar to the Wisconsin cohort. While the age-specific prevalence of *Pa* rose dramatically from 30% at age <1 to >90% at age 7 in the Wisconsin cohort, it was stable at 17 to 26% for each year of age in our cohort, perhaps reflecting the efficacy of *Pa* eradication therapies, infection control and other improvements in CF care over the past 20 years. In Wisconsin, non-mucoid *Pa* preceded mucoid *Pa* in all participants. The large size of our contemporary cohort, the variable specimen types cultured for *Pa* (predominantly oropharyngeal swabs), and the variability between sites in interpreting and recording mucoidy might partially explain why we observed some cases of mucoid *Pa* acquisition at the time of initial *Pa*. While the prevalence of mucoid *Pa* reached 20% at age 8 and nearly 40% at age 10 in the

Wisconsin cohort, in our cohort the age-specific prevalence of mucoid *Pa* was no higher than 8% up to age 10 years. This difference in prevalence might imply that the transition time to mucoid *Pa* is longer now than it was 20 years ago, however, we did not have enough follow-up to determine overall median time to mucoidy, as only 8% of the cohort acquired mucoid *Pa*.

Not surprisingly, in Cox proportional hazards models, we found mucoidy to be a strong predictor of time to chronic *Pa* infection, though chronic *Pa* was not a predictor of mucoid *Pa*, perhaps because it was so much more common to develop mucoid *Pa* prior to chronic *Pa*. We also found high risk CFTR functional class (both mutations in class 1 to 3) to be a predictor of earlier acquisition of initial *Pa*, chronic *Pa* and mucoid *Pa* as well as shorter transition times from initial to both chronic and mucoid *Pa*. These results are concordant with our previous finding that high risk CFTR functional class was a risk factor for initial *Pa* acquisition in the EPIC Observational Study cohort (29), as well as the finding by Levy, et al that the number of F508 del alleles is a risk factor for mucoid *Pa* acquisition (30).

Strengths of our analysis include the large, nationally representative cohort and longitudinal observations. In addition, because cohort participants were born after 2003, the majority were diagnosed by newborn screening (widely adopted in U.S. states between 2003 and 2010), allowing a more complete picture of *Pa* patterns from very early in life than in prior studies.

Our study also has important limitations. First, almost all respiratory cultures (84%) were from the upper airway (oropharyngeal) in this largely non-sputum producing cohort, since routine bronchoalveolar lavage is not standard of care at U.S. CF centers. Oropharyngeal cultures are well known to have relatively good specificity and negative predictive value but poor sensitivity and positive predictive value for the presence of *Pa* in the lower respiratory tract (31). Furthermore, oropharyngeal cultures do not reliably predict lower airway genotypes (15). Therefore, our results may not be generalizable to lower airway *Pa* and may overestimate *Pa* prevalence. Secondly, the CFFPR does not capture data on *Pa* eradication treatment, so that we were unable to evaluate whether there was an association between antibiotic treatment of newly acquired *Pa* and risk of chronic or mucoid *Pa* in our cohort. This question has been previously addressed in the long term follow-up study of the EPIC Clinical Trial of *Pa* eradication regimens, in which children who achieved sustained eradication of *Pa* had significantly reduced risks of developing chronic *Pa* or mucoidy(16). Though we do not have individual-level data on *Pa* eradication regimens, we do have site-level results of annual surveys of the 59 U.S. CF centers participating in the EPIC Observational Study during the same era. In 2008, 79% of sites responded that they "always" prescribed anti-pseudomonal antibiotics for newly isolated *Pa* and an additional 15% stated that they "often" prescribed these antibiotics. Eradication antibiotics (not mutually exclusive) most commonly listed were inhaled tobramycin (98%) and oral ciprofloxacin (90%) (M. Rosenfeld, personal communication). Thus, *Pa* eradication regimens were in widespread use during the period of our study.

Another limitation is that our follow up period was relatively short (less than 6 years on average). We were therefore unable to determine the median time from incident to mucoid or

chronic *Pa*, and had too little follow up after mucoid or chronic *Pa* to meaningfully evaluate clinical outcomes associated with chronic or mucoid *Pa*. Follow-up time and culture frequency also varied between individuals, potentially introducing length and sampling biases, respectively: those with longer observation or more frequent sampling are at higher risk of detection of *Pa*. Mucoidy was evaluated by each site's clinical microbiology lab, potentially introducing misclassification and may have been the reason we observed lower mucoidy prevalence than other reports. Our observation that mucoidy in some instances preceded chronic infection was in part due to our definition of chronic *Pa* infection, which was achieved at the *end* of a year in which ≥3 quarters of cultures were *Pa*+. Among the 150 cases in which mucoidy preceded the chronic stage, the mean (SD) time from mucoid to chronic *Pa* was 1.7 (1.8) years with a median of 0.75 years (range 0.25, 7.5 years), suggesting that in most of those cases, mucoidy appeared at the beginning of the year in which chronic infection developed. Finally, defining chronic *Pa* in our cohort is imperfect because of differential follow-up, relatively low culture frequency, and culture type (primarily oropharyngeal). We showed that 27% of those who met the definition of chronic *Pa* became *Pa* free in the following year, suggesting that our definition of chronic *Pa* is somewhat liberal.

In conclusion, in this contemporary large national cohort of young children with CF, we found the initial acquisition of *Pa* was common and occurred at an age very similar to that observed prior to the widespread use of *Pa* eradication regimens, likely reflecting the fact that *Pa* is initially acquired from the environment. Though our patients were young and the follow up period relatively brief, we nonetheless observed emergence of chronic *Pa* in 8% and mucoid *Pa* in 11%. More sensitive *Pa* detection techniques, better infection control and improved *Pa* eradication regimens could potentially decrease rates of early chronic and mucoid *Pa* and thus improve outcomes in children with CF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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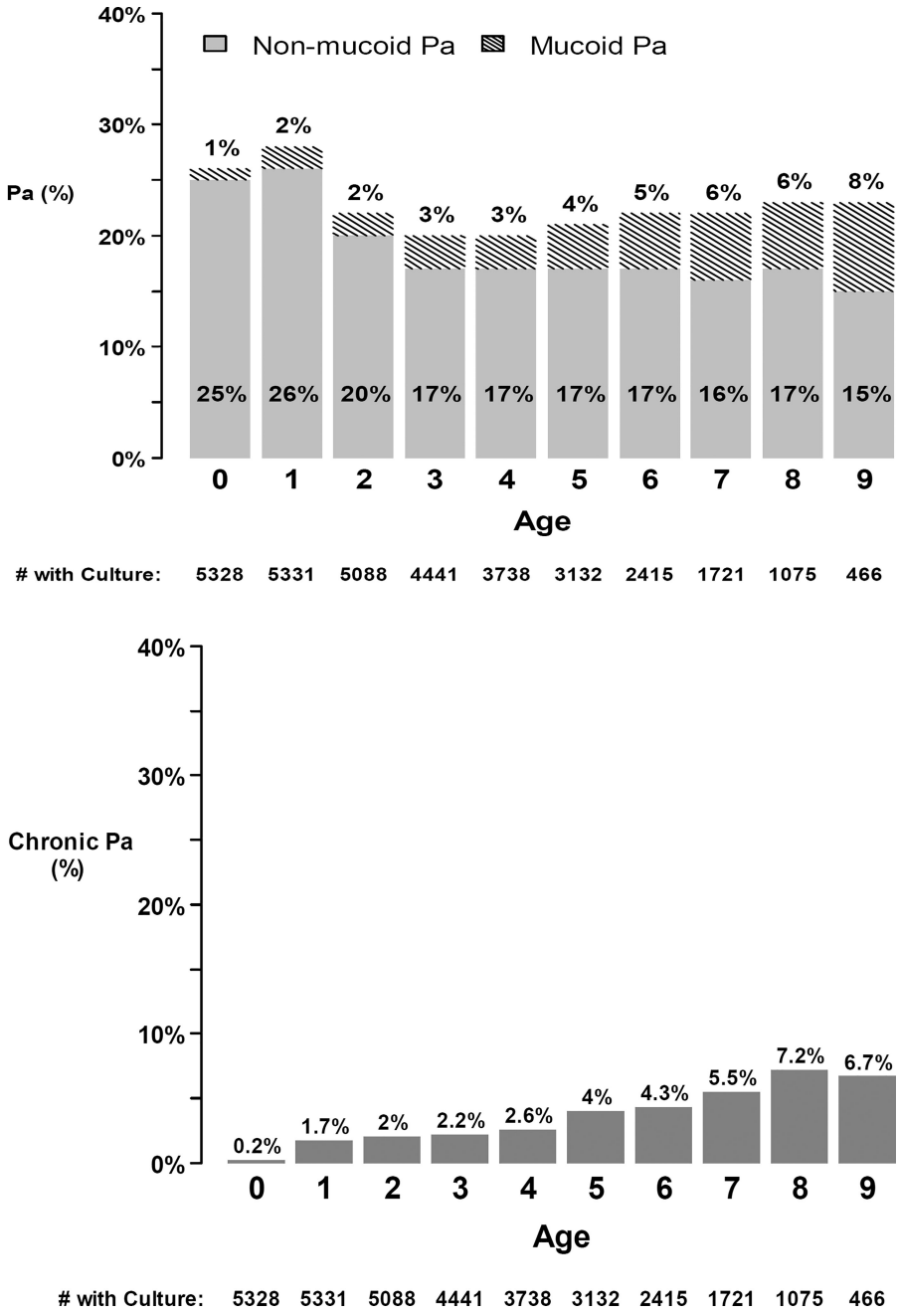

Figure 1. a–b. *Pa* prevalence by age

Panel **a)** overall *Pa* prevalence (entire bar) and mucoid *Pa* prevalence (hashed bar), and panel **b)** chronic *Pa* prevalence. Denominator of number at risk along the bottom

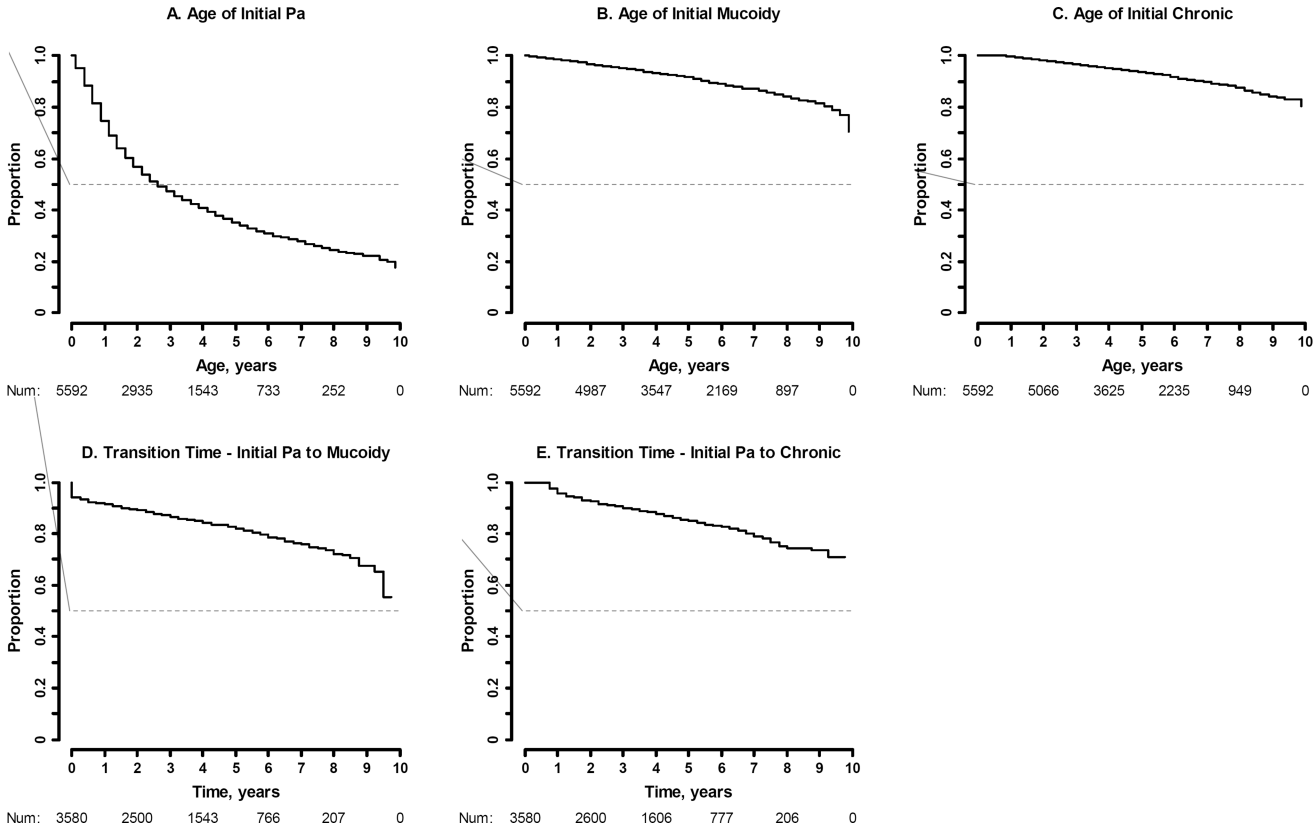

Figure 2. a–e. Kaplan-Meier curves for acquisition of *Pa*

a) Age of initial *Pa* b) age of initial mucoid *Pa*, c) age of initial chronic *Pa*, d) transition time from initial non-mucoid to mucoid *Pa*, and e) transition time from initial to chronic *Pa*.

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Table 1

CF Patient Cohort Demographic and clinical characteristics: overall and by *Pa* stage

	All	Remained *Pa* Free	Ever *Pa* Positive	Ever Mucoid *Pa*[a]	Ever Chronic *Pa*[a]
Demographics	**N=5,592**	**N=2,012**	**N=3,580**	**N=594**	**N=455**
Female, n (%)	2,762 (49%)	998 (50%)	1,764 (49%)	308 (52%)	222 (49%)
Race, n (%):					
White/Caucasian	4,979 (89%)	1,808 (90%)	3171 (89%)	523 (88%)	392 (86%)
African-American	213 (4%)	74 (4%)	139 (4%)	26 (4%)	23 (5%)
Other	400 (7%)	130 (6%)	270 (8%)	45 (8%)	40 (9%)
Hispanic n (%)	596 (11%)	201 (10%)	395 (11%)	92 (15%)	69 (15%)
Diagnosis by, n (%):					
Prenatal Screening	275 (5%)	109 (5%)	166 (5%)	20 (3%)	28 (6%)
Meconium Ileus/Obstruction	948 (17%)	284 (14%)	664 (19%)	107 (18%)	96 (21%)
Newborn Screening	3,424 (61%)	1,349 (67%)	2075 (58%)	289 (49%)	217 (48%)
Other/Unknown	945 (17%)	270 (13%)	675 (19%)	178 (30%)	114 (25%)
Del F508 Genotype, n (%):					
Homozygous	2,627 (47%)	800 (40%)	1827 (51%)	327 (55%)	253 (56%)
Heterozygous	2,248 (40%)	924 (46%)	1324 (37%)	181 (30%)	145 (32%)
Other/Unknown	717 (13%)	288 (14%)	429 (12%)	86 (14%)	57 (13%)
CFTR Mutation Class, n (%):					
2 class I–III alleles	4,023 (72%)	1,285 (64%)	2738 (76%)	469 (79%)	368 (81%)
at least 1 class IV–V allele	513 (9%)	296 (15%)	217 (6%)	23 (4%)	16 (4%)
Other/Unknown	1,056 (19%)	431 (21%)	625 (17%)	102 (17%)	64 (14%)
Age at CF diagnosis					
mean (SD)	0.09 (0.22)	0.09 (0.20)	0.10 (0.22)	0.13 (0.28)	0.13 (0.28)
Age of last respiratory culture recorded in CFFPR, yrs					
mean (SD)	5.47 (2.46)	4.59 (2.41)	5.96 (2.35)	6.94 (2.08)	6.96 (2.04)

[a]Note that 223 had both mucoid *Pa* and chronic *Pa* thus these subsets are not mutually exclusive.

Table 2

Transition pattern from initial *Pa* to chronic *Pa* and mucoid *Pa* among: those with any *Pa* (N=3,580); those with any Chronic *Pa* (N=455); and those with any Mucoid *Pa* (N=594)

	Ever *Pa* Positive (N=3,580)	Ever Chronic *Pa* (N=455)	Ever Mucoid *Pa* (N=594)
Initial *Pa* Only	2754 (77%)	–	–
Initial Pa → Chronic Only	232 (6%)	232 (51%)	–
Initial Pa → Mucoid Only	371 (10%)	–	371 (62%)
Initial Pa → Mucoid & Chronic co-occur	11 (<1%)	11 (2%)	11 (2%)
Initial Pa → Chronic → Mucoid	62 (2%)	62 (14%)	62 (10%)
Initial Pa → Mucoid → Chronic	150 (4%)	150 (33%)	150 (25%)

Note: transitions indicate first occurrence of chronic or mucoid Pa