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Standard Care versus Protocol Based Therapy for New Onset *Pseudomonas aeruginosa* in Cystic Fibrosis

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Abstract

Rationale—The Early *Pseudomonal* Infection Control (EPIC) randomized trial rigorously evaluated the efficacy of different antibiotic regimens for eradication of newly identified *Pseudomonas* (*Pa*) in children with cystic fibrosis (CF). Protocol based therapy in the trial was provided based on culture positivity independent of symptoms. It is unclear whether outcomes observed in the clinical trial were different than those that would have been observed with historical standard of care driven more heavily by respiratory symptoms than culture positivity alone. We hypothesized that the incidence of *Pa* recurrence and hospitalizations would be significantly reduced among trial participants as compared to historical controls whose standard of care preceded the widespread adoption of tobramycin inhalation solution (TIS) as initial eradication therapy at the time of new isolation of *Pa*.

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*The names and affiliations of the Early Pseudomonas Infection Control (EPIC) and Epidemiologic Study of Cystic Fibrosis (ESCF) Investigators are listed in the Appendix.

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Methods—Eligibility criteria from the trial were used to derive historical controls from the Epidemiologic Study of CF (ESCF) who received standard of care treatment from 1995 to 1998, before widespread availability of TIS. *Pa* recurrence and hospitalization outcomes were assessed over a 15-month time period.

Results—As compared to 100% of the 304 trial participants, only 296/608 (49%) historical controls received antibiotics within an average of 20 weeks after new onset *Pa*. *Pa* recurrence occurred among 104/298 (35%) of the trial participants as compared to 295/549 (54%) of historical controls (19% difference, 95% CI: 12%, 26%, p<0.001). No significant differences in the incidence of hospitalization were observed between cohorts.

Conclusions—Protocol-based antimicrobial therapy for newly acquired *Pa* resulted in a lower rate of *Pa* recurrence but comparable hospitalization rates as compared to a historical control cohort less aggressively treated with antibiotics for new onset *Pa.*

Keywords

Cystic fibrosis; *Pseudomonas aeruginosa*; early intervention; randomized trial; historical controls

Introduction

The clinical impact of chronic infection with *Pseudomonas aeruginosa* (*Pa*) on morbidity and mortality is well established among individuals with cystic fibrosis (CF)[1, 2]. Treatment with anti-pseudomonal antibiotics to delay or prevent chronic *Pa* infection is critical during the early infection period because of a limited “window of opportunity” during which *Pa* infection is characterized by non-mucoid phenotype, antibiotic sensitivity, and low density[3-9]. Over the last decade, many studies have demonstrated the microbiologic efficacy of initial *Pa* eradication regimens [10-15], and the standard of care has thus transitioned to treating *Pa* positive cultures independent of concurrent symptoms [16-18]. Treggiari et. al.[19] reported that among 146 pediatric CF clinical centers in the United States in 2003, 93% of children who received anti-pseudomonal treatment at first *Pa* infection were asymptomatic at the time of presentation. Only two placebo-controlled studies have been performed to assess the impact of initial eradication therapy on microbiologic outcomes[11, 12, 14], but both were limited to small sample sizes and did not evaluate impact of this therapy on clinical outcomes.

The Early *Pseudomonas* Infection Control (EPIC) randomized trial was designed to rigorously evaluate the impact of four different early anti-pseudomonal treatment regimens on long term clinical and microbiologic efficacy outcomes in a large cohort of CF children less than 13 years of age with recent isolation of *Pa* from respiratory cultures [19, 20]. Over an 18-month period, the trial compared the effects of cycled antibiotic therapy administered in quarterly cycles regardless of results of quarterly respiratory cultures or symptoms with culture-based therapy administered only when *Pa* was isolated from quarterly cultures. All participants received an initial antibiotic course at study entry consisting of 28 to 56 days of tobramycin inhalation solution (TIS) with or without oral ciprofloxacin to promote initial *Pa* eradication. The trial revealed no differences between treatment regimens with respect to key microbiologic and clinical outcomes including *Pa* recurrence, pulmonary exacerbations,

and hospitalizations [21]. The overall low rate of *Pa* recurrence (35%) and hospitalization (26%) observed in the 18-month trial contributed to the subsequent recommendation of use of initial therapy with TIS at the time of new onset *Pa* followed by close microbiologic surveillance[22]. However, due to the lack of a placebo-control in the trial, negative cultures following the initial cycle could have reflected spontaneous clearance rather than efficacy of the targeted therapeutic approach[22]. As antimicrobial treatment based on culture positivity alone to eradicate newly isolated *Pa* became standard of care in the U.S. in the early 2000s, a control group receiving placebo and only symptom-based anti-pseudomonal antibiotic therapy was not considered ethical at the time of trial initiation in 2004[20]. It thus remains unclear whether microbiologic and clinical outcomes observed in the clinical trial, including relatively low *Pa* recurrence and hospitalization rates, were different than those that would have been observed with treatment of *Pa* driven more heavily by the presence of respiratory symptoms than on culture positivity alone.

The objectives of the present study were to compare key outcomes between children enrolled in the EPIC trial who were treated with a standardized *Pa* eradication protocol and historical controls observed prior to the widespread adoption of an anti-pseudomonal eradication regimen and from an era in which treatment of *Pa* was driven primarily by the presence of respiratory symptoms[14]. In the absence of the ability to compare to placebo, the availability of historical controls provides a unique opportunity to evaluate the effectiveness of standardized eradication therapies as has been done in a prior study of inhaled colistin[23]. Our primary hypothesis was that both the frequency of *Pa* recurrence, defined as the first positive culture after an initial therapy period, and occurrence of hospitalizations would be significantly reduced in the clinical trial cohort who received a standardized, protocol based therapy with TIS as compared to the historic controls.

Materials and Methods

Cohort Selection

The trial cohort was comprised of 304 eligible and randomized participants in the EPIC clinical trial as previously described[20] (ClinicalTrials.gov number NCT00097773). Eligibility criteria from the clinical trial were used as the primary selection criteria for the historical control cohort (E-Table 1, Online Supplement).

The historical control cohort was obtained from the Epidemiologic Study of Cystic Fibrosis[24] (ESCF), a prospective encounter-based observational study initiated in 1994 and designed to characterize the natural history and medication usage of over 30,000 participants with CF, providing the most comprehensive historical data for comparison with the EPIC trial cohort. Controls who met the eligibility criteria outlined in E-Table 1 during the years 1995 to 1998 were selected in order to reflect treatment practices before the widespread commercial availability of TIS[25]. To achieve a larger sample size and increase precision, a 2:1 matching strategy based on age and gender was used to identify 608 controls to compare with the 304 clinical trial participants.

This study was approved by the Institutional Review Board (IRB) at Seattle Children's Hospital, Seattle, Washington. Written informed consent was obtained from participants or their guardians as required by the IRBs at the participating institutions.

Study Design

Based on the date of the new *Pa* culture which defined eligibility into each of the cohorts (E-Table 1), two distinct data collection periods were defined: the initial therapy period and the follow-up period (Figure 1). The initial therapy period enabled characterization of the early treatment response to antimicrobial therapy directed against new onset *Pa.* For EPIC clinical trial participants, the initial therapy period was defined as the time between new onset *Pa* and up to 10 weeks following the baseline visit in the clinical trial. The clinical trial allowed up to a 6-month window between the new onset *Pa* culture that defined eligibility and the baseline visit, during which time participants could receive one course of anti-pseudomonal antibiotics. After randomization and during the first quarter of the trial, all participants were given 1-2 courses of anti-pseudomonal antibiotics to promote initial *Pa* eradication, irrespective of treatment group assignment[20]. For the ESCF controls, the length of the initial therapy period for each control was determined based on that of their matched clinical trial participant starting from the time of new onset *Pa.* The follow up period for each clinical trial participant was defined as the time between the end of the initial therapy period (approximately 10 weeks into the clinical trial) and the day of their final study visit at approximately 70 weeks post-randomization (Figure 1). The follow up times were derived for each EPIC clinical trial participant and similarly used to derive matched follow up periods for their ESCF historical controls.

Study Endpoints

The primary endpoint for comparison between cohorts was the proportion with recurrent *Pa*, defined as at least one positive respiratory culture for *Pa* during the follow up period, and the secondary endpoint was the proportion of participants hospitalized for any reason during the follow up period.

Statistical Methods and Precision

Demographic and baseline clinical characteristics of the cohorts were summarized descriptively in conjunction with the frequency of anti-pseudomonal antibiotic usage. The proportions of participants with *Pa* recurrence and with hospitalization were summarized for each cohort with corresponding 95% confidence intervals derived using the Newcombe-Wilson method[26], and p-values for differences between cohorts were obtained using a two-sided 0.05 level of significance Fisher exact test. Due to the exploratory nature of this study, no formal hypothesis testing was performed and an *a priori* precision estimate utilizing a confidence interval approach was derived for the primary comparison of interest. A total of 104/298 (35%) of participants in the clinical trial experienced *Pa* recurrence after the initial therapy period. Assuming this proportion is 10% higher among the 608 ESCF historical controls, the 95% confidence intervals corresponding to the 10% difference would be (3%, 17%). Analyses were performed using the statistical software SAS, version 9.1.3 (SAS

Institute Inc., Cary, NC), R statistical package version 2.9.1 (R Foundation for Statistical Computing, Vienna, Austria), and Stata version 10.1 (StataCorp LP, College Station, TX).

Sensitivity Analysis

Under the hypothesis that the clinical trial cohort would have better outcomes than the historical controls, a sensitivity analysis was performed to assess whether a result of better outcomes among clinical trial participants could be explained merely by clinical trial participation bias. To evaluate this potential bias, the outcomes of *Pa* recurrence and hospitalization were also assessed among a concurrent observational control cohort not enrolled in a clinical trial and obtained from the EPIC observational study, an ancillary study to the Cystic Fibrosis Foundation National Patient Registry[20]. This longitudinal observational study was conducted in parallel with the EPIC clinical trial at the same sites and enrolled 1787 children with CF <13 years of age never colonized with *Pa* or negative for *Pa* for at least 2 years prior to enrollment. Participants who turned *Pa* positive were offered enrollment in the EPIC clinical trial. All children (n=231) who were eligible for the clinical trial based on eligibility criteria for new onset *Pa* as defined for the clinical trial (E-Table 1), but did not enroll, comprised the concurrent control cohort with which sensitivity analyses were performed.

Results

Baseline Characteristics and Follow-Up Time

The EPIC clinical trial cohort was comprised of 304 participants with demographic and baseline clinical characteristics summarized in Table 1. Notably, FEV_1 % predicted in the historical controls was significantly lower than the trial participants (p=0.004). The number of visits recorded during the initial therapy and follow-up periods were well balanced between the cohorts with an average of 3 visits during the 4.6 month initial therapy period in the clinical trial cohort as compared to 2.4 visits in the historical controls. During the follow-up period, an average of 5.6 visits were available from the clinical trial cohort over an average 13 months as compared to 4.9 visits from the historical controls over the comparable time period.

Antibiotic Use in the Initial Therapy Period

There were significant differences in antibiotic usage between the cohorts during the initial therapy period (Table 2). By design, all 304 (100%) of the clinical trial participants received inhaled antibiotics, specifically TIS. In contrast, only 184/608 (30%) of the historical controls had documented use of inhaled antibiotics, of whom 129/184 (70%) used TIS. Of the 227 (75%) EPIC trial participants who received oral antibiotics, 152/227 (67%) received oral ciprofloxacin as a protocol-based therapy in combination with TIS. In contrast, 114/608 (19%) of historical controls received oral antibiotics, with the majority receiving oral quinolones (69/114 [61%]). Use of IV antibiotics during the initial therapy period among the historical controls was slightly higher than that among the EPIC trial participants with 108/608 (18%) historical controls having documented use as compared to 31/304 (10%) EPIC trial participants.

Antibiotic Use in the Follow-Up Period

Similar trends in antibiotic use were observed throughout the follow up period among the clinical trial participants, with 289/304 (95%) using inhaled, oral, or IV antibiotics (Table 2). Significant differences in antibiotic use remained between the EPIC trial participants and the ESCF historical controls, with 37% fewer (95% CI: -41%, -32%) historical controls, or 58% overall, using antibiotics during the follow up period.

Pa Recurrence

While the majority of clinical trial participants had 4 or more cultures available during the follow up period, this was not the case for the historical controls and thus *Pa* recurrence rates are reported both overall and stratified by culture frequency (Table 3). Overall, 104/298 (35%) of trial participants experienced *Pa* recurrence during the clinical trial. In contrast, 295/549 (54%) of historical controls had *Pa* recurrence (19% difference, 95% CI: 12%, 26%, $p<0.001$). Importantly, the differences in *Pa* recurrence rates were consistent across the differing culture frequencies (Table 3). *Pa* recurrence rates did not significantly differ between historical controls who received antibiotics in the initial therapy period and those who did not (135/269 [50%] vs. 160/280 [57%] respectively, 7% difference, $p=0.11$). There was also a striking difference between EPIC trial participants and historical controls in terms of the proportion who developed persistent *Pa* infection, defined as at least two positive cultures during the follow-up period, with 49/292 (17%) of EPIC trial participants developing persistent *Pa* infection as compared to 129/396 (33%) of historical controls (16% difference, 95% CI 9%, 22%, $p<0.001$).

Hospitalizations

Despite significant differences between EPIC trial participants and historical controls in early antibiotic use at new onset *Pa*, no significant difference in subsequent all cause hospitalization was observed. A total of 79/304 (26%) of EPIC trial participants were hospitalized during the follow up compared to 124/608 (20%) of the historical controls (difference 6%, 95% CI: 0%,12%, $p=0.06$). Hospitalization rates were slightly higher however among historical controls who received antibiotics during the initial therapy period with 72/296 (24%) hospitalized as compared to 52/312 (17%) historical controls who did not receive antibiotics during the initial therapy period (7%, difference, 95% CI 1%,14%, $p=0.02$).

Sensitivity Analyses

There were 231 children from participating sites of the clinical trial who were enrolled in the concurrent EPIC observational study, experienced new onset *Pa* during the trial enrollment period, and who did not enroll in the clinical trial. The mean age of the cohort was 6.2 years (SD=3.4). The primary reason for non-enrollment into the trial was the family declining to participate (105/231, 46%) with an additional 29/231 (13%) not approached for enrollment into the trial and the remainder providing unknown reasons for non-enrollment. A total of 152/231 (66%) received antibiotic therapy within the first few months following new onset *Pa*. Comparable to the trial participants, nearly all received at least one course of antibiotics over the follow up period (n=194/231, 84%). *Pa* recurrence and hospitalization outcomes

were comparable between the trial participants and non-participants with 79/229 (34%, 95% CI: 28%, 40%) of non-trial participants with culture results available experiencing *Pa* recurrence and 49/231 (21%, 95% CI: 16%, 27%) hospitalized during the follow up period following new onset *Pa.* These rates were not significantly different between those receiving antibiotics during the initial therapy period and those not receiving antibiotics during the initial therapy period. Unlike the trial participants for whom the majority (91%) had 4 or more cultures during the follow-up period, only 119/231 (75%) had 4 or more cultures among the non-trial participants.

Discussion

This study provides a unique opportunity to evaluate the results from a randomized clinical trial studying the effectiveness of protocol-based anti-pseudomonal treatment regimens for new onset *Pa* among children with CF versus historic, less standardized treatment approaches. We hypothesized that trial participants who received anti-pseudomonal therapy in response to new onset *Pa* according to a study protocol would have improved outcomes in comparison to a standard of care used before the aggressive use of an initial eradication therapy. We documented that the approach to treatment of early *Pa* infection has changed over the past 15 years in the U.S with significantly higher use of both inhaled and oral antibiotics. This change towards earlier and more frequent antibiotic use was associated with significantly lower *Pa* recurrence rates in the clinical trial participants as compared to the historical controls. This result is consistent with those from other studies regarding the efficacy of inhaled antibiotics in initial eradication therapy among young children with CF[10-15, 23]. Failure to initially eradicate *Pa* and frequent *Pa* recurrence has also been associated with higher risk of developing an acute pulmonary exacerbation, and thus the recurrence of *Pa* is an important outcome indicative of the transition to chronic *Pa* infection and its associated morbidity [27].

Despite significant differences in the use of antibiotics for new onset *Pa* between clinical trial participants and historical control cohorts, no significant differences in hospitalization rates were observed. Another clinically relevant endpoint would have been pulmonary exacerbations, as this endpoint is more specific to respiratory infections and can capture less severe events than those requiring hospitalization; however, inconsistency in the definition of exacerbation across the cohorts did not allow the use of this endpoint in this study[28]. IV antibiotic treatment is often a surrogate for more severe pulmonary exacerbations. However, as with the hospitalization endpoint, it was not significantly different between the cohorts following initial treatment for new onset *Pa.* These results suggest that differences in *Pa* culture positivity between the cohorts did not translate into differences in clinical outcome as captured by hospitalizations over the course of the study follow-up.

Our sensitivity analysis utilizing concurrent controls from the EPIC observational study suggests that the protocol based therapy given during the clinical trial for *Pa* eradication resulted in similar clinical and microbiologic outcomes as compared to the control cohort not participating in the trial and receiving contemporary standard of care treatment. We documented that contemporary treatment with increased use of early anti-pseudomonal antibiotics was associated with a reduction in the frequency of *Pa* recurrence as compared

with the historical controls. This is a key result needed to benchmark the outcomes observed in the clinical trial, and confirm that trial results were not due to trial participation bias.

There are several limitations to our study, in particular that differences between the trial cohort and historical controls may be attributable to other differences in care between the cohorts that have been introduced over the years including changes in infection control practices, changes in use of chronic therapy, and improvements in nutritional care. Further, antibiotic use and isolation of *Pa* from respiratory cultures may have been underestimated in the historical controls. Specifically, there were differences in culture frequency between the cohorts that could have resulted in under-detection of *Pa* among the historical controls, and thus our estimate of the difference between the cohorts in *Pa* recurrence rates may be an underestimate of the true difference in rates. In addition, although the historic controls were chosen based on eligibility criteria similar to those utilized in the clinical trial for the definition of new onset *Pa*, there were some secondary inclusion and exclusion criteria that were not available. Lack of availability of lifetime history of *Pa* positivity prior to the initiation of ESCF for the historical controls, and lung function for younger children, precluded us from being able to match on these potentially important factors. Thus, the historical control cohort may be different than the trial participants in terms of other unmeasurable characteristics. It is uncertain however whether any selection bias in the historic control cohort would induce better or poorer outcomes.

This study evaluates the results of a non-placebo controlled clinical trial compared to historical standard of care, and demonstrates the shift in approach to treatment of early *Pa* infection in the U.S. in the past 15 years and the impact of these changes on microbiologic and clinical outcomes. The use of observational registries for studies such as this is critical in the orphan disease setting and enables evaluation of the generalizability of the results of a clinical trial. The ability of this study to benchmark the EPIC clinical trial results ultimately demonstrates that the protocol based therapy received during the trial is effective in preventing *Pa* recurrence when compared with less aggressive antibiotic therapy following acquisition of *Pa.*

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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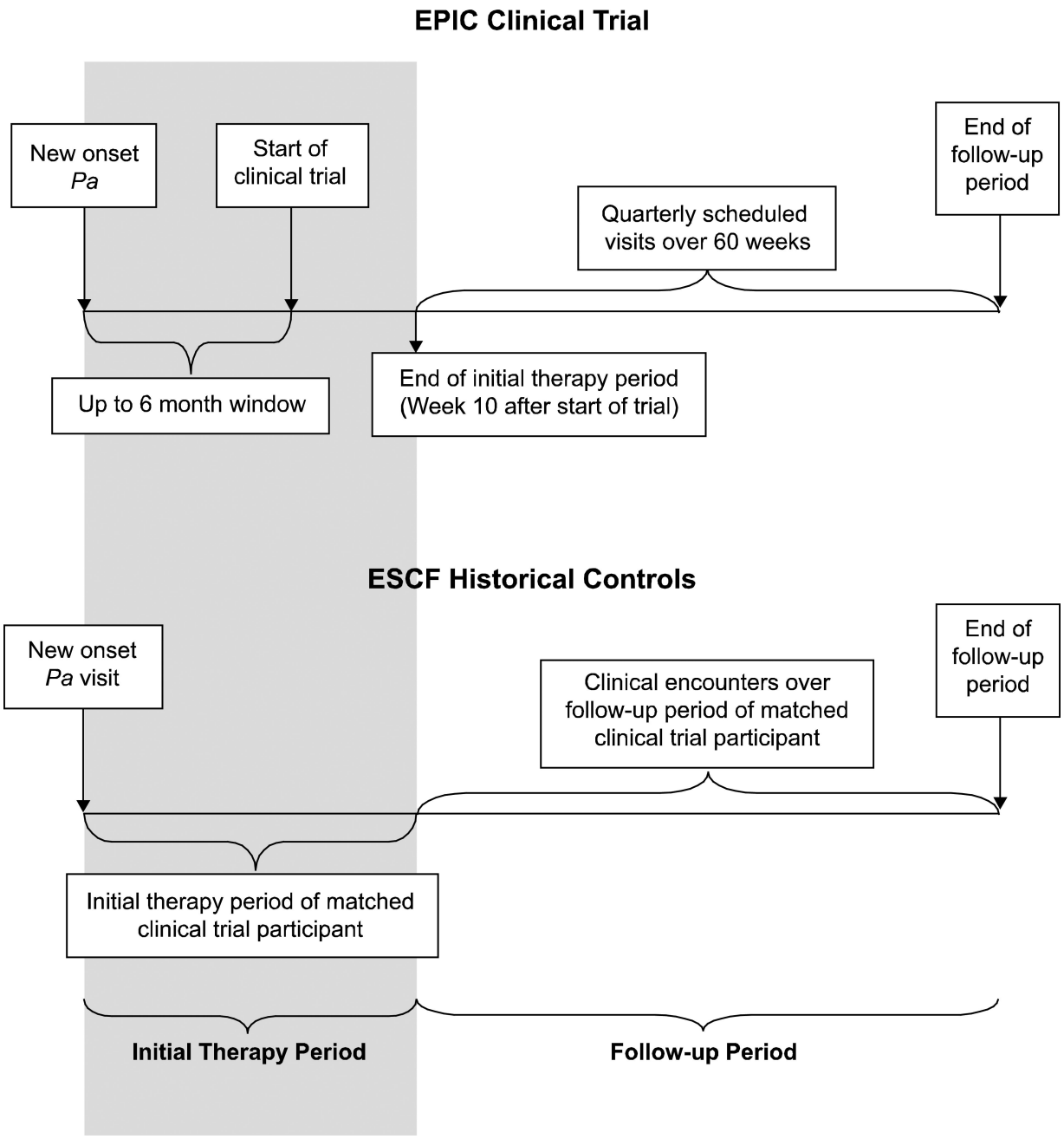

Figure 1. Schematic of Data Collection and Timing

The initial therapy period for the EPIC clinical trial participants was defined as the time between the *Pa* qualifying culture and 10 weeks post their baseline visit in the clinical trial. The clinical trial allowed up to a 6-month window between the new onset *Pa* that defined eligibility and the baseline randomization visit and during this time, participants were allowed limited anti-pseudomonal antibiotics.[20] For the historical controls, the length of the initial therapy period for each control was determined based on that of their matched clinical trial participant. The follow up period for each clinical trial participant was defined as the time between the end of the initial therapy period (approximately 10 weeks into the

clinical trial) and the day of their final study visit at approximately 70 weeks post-randomization. The follow up times were derived for each clinical trial participant and similarly used to derive matched follow up periods for the controls.

Table 1

Demographic and Baseline Clinical Characteristics

	EPIC Clinical Trial (N=304)	ESCF Historical Controls (N=608)
Gender, n (%)		
Female	154 (50.7)	308 (50.7)
Race*, n (%)		
White (non-Hispanic)	285 (93.8)	544 (89.5)
Black (non-Hispanic)	7 (2.3)	19 (3.1)
Hispanic	4 (1.3)	32 (5.3)
Other/Mixed/Unknown	8 (2.6)	13 (2.1)
Genotype, n (%)		
Delta F508 Homozygous	149 (49.0)	266 (43.8)
Delta F508 Heterozygous	116 (38.2)	165 (27.1)
Other	24 (7.9)	30 (4.9)
Unknown	15 (4.9)	147 (24.2)
Age at New Onset *Pa*, yrs		
Mean (SD)	5.5 (3.5)	5.5 (3.5)
Min, Max	0.1, 13.0	0.50, 12.96
Age Group, years, n (%)		
1-3	93 (30.6)	189 (31.1)
>3-6	91 (29.9)	174 (28.6)
>6-12	120 (39.5)	245 (40.3)
FEV_1 (% Predicted)†*		
n	155	230
Mean (SD)	96.2 (16.7)	90.9 (18.3)
Min, Max	28.9, 130.5	26.9, 142.7

* $p<0.05$

† Spirometry measures are only available for those old enough to perform the procedure and corresponded to the closest visit on or after new onset *Pa*.

Table 2

Summary of antibiotic therapy received during the initial therapy and follow-up periods after new onset *Pa*.

	EPIC Clinical Trial (N=304)	ESCF Historical Controls (N=608)
INITIAL THERAPY PERIOD[1]		
Inhaled Antibiotics		
No. (%) Participants	304 (100%)	184 (30.3%)
Oral Antibiotics		
No. (%) Participants	227 (74.7%)	114 (18.8%)
IV Antibiotics		
No. (%) Participants	31 (10.2%)	108 (17.8%)
Any Antibiotic		
No. (%) Participants	304 (100%)	296 (48.7%)
95% CI	(98.8%, 100%)	(44.7%,52.7%)
Diff. as Compared to Trial		
Participants	-	−51.3%
95% CI	-	(−55.3%,−47.2%)
p-value		<0.001
FOLLOW UP PERIOD[2]		
Inhaled Antibiotics		
No. (%) Participants	218 (71.7%)	241 (39.6%)
Oral Antibiotics		
No. (%) Participants	276 (90.8%)	174 (28.6%)
IV Antibiotics		
No. (%) Participants	62 (20.4%)	113 (18.6%)
Any Antibiotic		
No. (%) Participants	289 (95.1%)	355 (58.4%)
95% CI	(92.0%,97.0%)	(54.4%,62.2%)
Diff. as Compared to Trial		
Participants	-	−36.7%
95% CI	-	(−41.1%,−31.8%)
p-value		<0.001

IV=Intravenous; CI=Confidence Interval

[1]The initial therapy period for the EPIC clinical trial participants was defined as the time between the *Pa* qualifying culture and 10 weeks post their baseline visit in the clinical trial. For the ESCF controls, the length of the initial therapy period for each control was determined based on that of their matched clinical trial participant.

[2]The follow up period for each clinical trial participant was defined as the time between the end of the initial therapy period (approximately 10 weeks into the clinical trial) and the day of their final study visit at approximately 70 weeks post-randomization. The follow up times were derived for each clinical trial participant and similarly used to derive matched follow up periods for the controls.

Table 3

Proportion of participants with recurrent *Pa* by the number of cultures obtained during the follow-up period.

	EPIC Clinical Trial (N=304)	ESCF Historical Controls (N=608)
No. (%) with Recurrent *Pa*		
Among those w/1 culture	0/6 (0%)	69/153 (45.1%)
Among those w/2 cultures	1/5 (20.0%)	79/148 (53.4%)
Among those w/3 cultures	1/10 (10.0%)	47/83 (56.6%)
Among those w/4+ cultures	102/277 (36.8%)	100/165 (60.6%)
Overall	104/298 (34.9%)	295/549 (53.7%)
95% CI	(29.7%,40.5%)	(49.6%,57.9%)
Overall Diff. as Compared		
to Trial Participants	-	18.8%
95% CI	-	(11.9%,25.5%)
		p<0.001

CI= Confidence Interval; Diff = Difference