Impact of Sustained Eradication of New *Pseudomonas aeruginosa* Infection on Long-term Outcomes in Cystic Fibrosis

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(See the Editorial Commentary by Zemanick and Laguna on pages 716–8.)

Background. *Pseudomonas aeruginosa* (*Pa*) is the most important pathogen infecting the airways in individuals with cystic fibrosis. A key question is whether children with newly acquired *Pa* infection who are able to achieve sustained eradication after early antipseudomonal therapy demonstrate improved long-term health outcomes compared with those who are unable to achieve a sustained microbiologic response.

Methods. This cohort study utilized observational follow-up data on children participating in the Early *Pseudomonas* Infection Control trial who received standardized therapy for newly acquired *Pa.* Sustained eradicators were defined as those who maintained *Pa*-negative cultures for 12 months after initial antipseudomonal therapy. Associations between eradication status and outcomes were assessed.

Results. Of the 249 trial participants included in the study, 172 (69%) achieved sustained eradication of *Pa* during the trial (sustained eradicators). Over the median 5-year follow-up, sustained eradicators had a 74% reduced risk of developing chronic *Pa* (hazard ratio [HR], 0.26; 95% confidence interval [CI], .17–.40) and a 57% reduced risk of mucoidy (HR, 0.43; 95% CI, .25–.73) compared with nonsustained eradicators. Sustained eradicators had significantly less anti-*Pa* antibiotic usage during follow-up compared with nonsustained eradicators. There was no association between eradication status and clinical outcomes including rate of exacerbation and lung function decline.

Conclusions. This is the first study to quantify the long-term durability of microbiological response associated with early antipseudomonal therapy, demonstrating the critical importance of optimizing antipseudomonal therapies during early *Pa* infection. The clinical impact of failure to achieve sustained *Pa* eradication remains unclear, however, and may be confounded by anti-*Pa* antibiotic usage.

Clinical Trials Registration. NCT00097773.

Keywords. *Pseudomonas* infections; *Pseudomonas aeruginosa*; cystic fibrosis; eradication therapy; treatment outcomes.

Pseudomonas aeruginosa (*Pa*) is perhaps the most important pathogen infecting the airways of individuals with cystic fibrosis (CF) [1, 2]. Early antibiotic treatment of newly acquired *Pa*, regardless of the presence of accompanying symptoms, is now considered standard of care to rapidly clear the pathogen and delay establishment of chronic infection [1, 3, 4]. However, the long-term impact of early antipseudomonal antibiotics on the progression of disease remains unclear. The majority of studies to date have focused on the comparison of clinical outcomes between those newly vs never infected with *Pa* [2, 5–9]; however, there is now a need to shift our efforts and determine the long-term clinical impact of current antipseudomonal treatment approaches for new *Pa*. A key clinical question is whether individuals

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with new *Pa* who are able to successfully achieve sustained *Pa* eradication after early antipseudomonal therapy at the time of new *Pa* acquisition demonstrate improved outcomes compared with those unable to achieve sustained eradication.

Consistent data across recent multicenter studies suggest that approximately one-third of children with CF and newly acquired *Pa* will fail to achieve sustained *Pa* eradication over a 1- to 2-year period after initial antipseudomonal therapy [10, 11], and yet there are limited data over a long duration of follow-up to quantify how their clinical progression of disease is affected. The Early *Pseudomonas* Infection Control (EPIC) clinical trial randomized children aged 1–12 years with newly acquired *Pa* to assess the efficacy of more aggressive vs less aggressive antipseudomonal therapy, and demonstrated no significant differences in outcomes between treatment regimens [10]. These children have been closely monitored for >5 years in an ongoing observational study, providing a unique opportunity to investigate the long-term impact of sustained *Pa* eradication [12].

The objectives of this study were to characterize *Pa* recurrence patterns among a contemporary cohort treated for newly acquired *Pa* and to compare those who achieved sustained eradication during the clinical trial with those who did not in terms of long-term microbiologic and clinical outcomes after completion of the clinical trial. We hypothesized that children who achieved sustained *Pa* eradication had a reduced risk of chronic *Pa* infection and mucoid *Pa* acquisition, reduced pulmonary exacerbation rates, and less rapid pulmonary function decline compared with participants who were unable to achieve sustained *Pa* eradication.

METHODS

Study Cohort and Definition of Sustained Eradication at Trial Completion

The cohort was comprised of participants from the EPIC Clinical Trial (ClinicalTrials.gov identifier NCT00097773) [10] who consented for follow-up in the EPIC observational study [12].

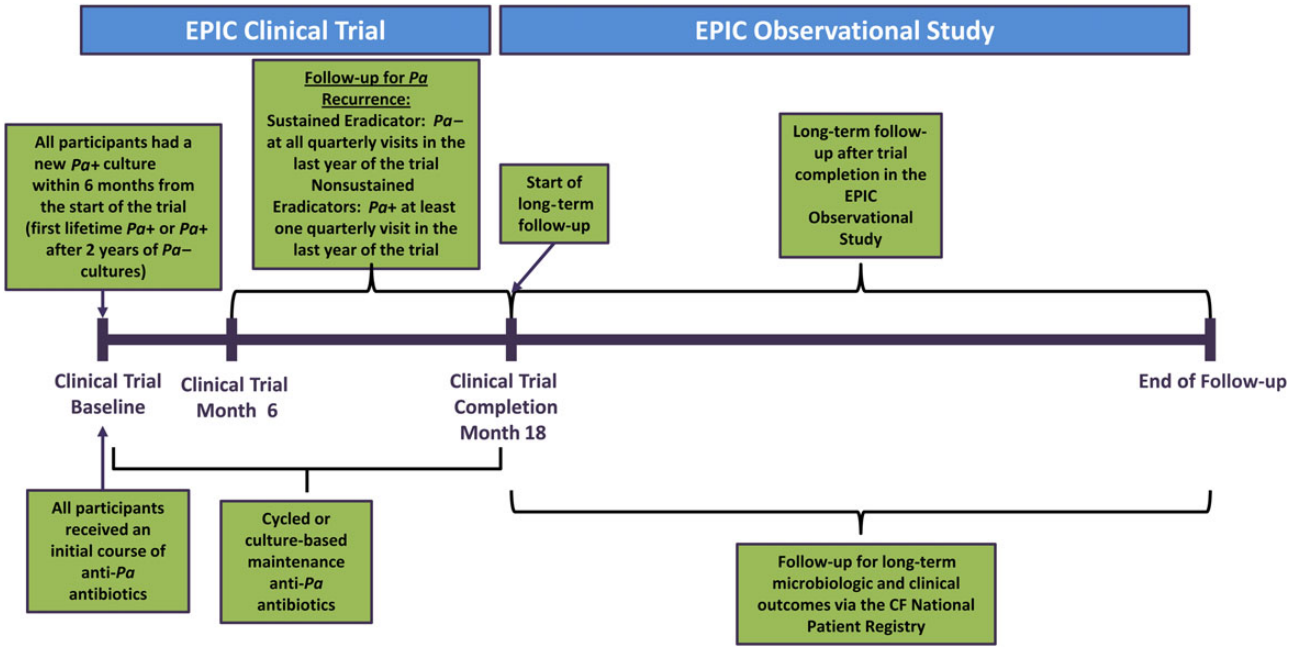

Figure 1. Overview of study design. Children with cystic fibrosis (CF) aged 1–12 years with newly identified *Pseudomonas aeruginosa* (*Pa*) infection within 6 months of enrollment were eligible for the trial. Newly identified *Pa* was defined as the first lifetime documented *Pa*-positive culture or a *Pa*-positive culture after a 2-year absence of *Pa* culture positivity (requiring at least 1 culture per year). For children aged 12–15 months, at least 1 *Pa*-positive culture since birth was required. Other eligibility criteria have been previously reported [12]. During the first quarter of the study, all children received initial *Pa* eradication treatment consisting of tobramycin inhalation solution, with half of the children randomly assigned to a concurrent course of oral ciprofloxacin and half to oral placebo. Children were randomized to 1 of 2 maintenance treatment strategies: (1) cycled therapy—treatment provided in quarterly cycles regardless of findings from scheduled quarterly respiratory cultures; or (2) culture-based therapy—treatment only in response to identification of *Pa* from quarterly cultures. Sustained *Pa* eradication was based on the Leeds definition of "*Pa*-free" [13] and required participants to have been *Pa* culture negative for at least 12 months prior to the completion of the trial (based on cultures obtained quarterly, with the average number of cultures for the cohort in the 12 months of the trial equal to 4.7). The assessment period for defining sustained *Pa* eradication allowed up to 6 prior months of intensive antipseudomonal therapy to achieve initial *Pa* eradication and was defined during the maintenance therapy phase of the trial. Long term follow-up was provided via the Early *Pseudomonas* Infection Control (EPIC) observational study and the CF National Patient Registry.

Key eligibility criteria and treatment received during the trial are shown in Figure 1 and have been previously described [12]. Participants were defined as "sustained eradicators" upon completion of the 18-month clinical trial if all quarterly cultures obtained during the preceding 12 months were free of *Pa* (Leeds definition of "*Pa*-free") [13]. This study was approved by the Institutional Review Board at Seattle Children's Hospital, Seattle, Washington.

Microbiologic and Clinical Outcomes After Trial Completion

Respiratory cultures during follow-up were performed at site clinical microbiology laboratories as part of standard clinical care, with results recorded in the Cystic Fibrosis Foundation National Patient Registry (CFFNPR). Microbiologic endpoints included time to first and second *Pa* recurrence and time to chronic *Pa*, defined as the third quarter in which a *Pa*-positive culture was observed within a 2-year period, which included retrospectively assessing cultures during the clinical trial period as applicable for earlier cultures during the follow-up period [14]. Time to mucoidy and resistant *Pa* were defined, respectively, as the first quarter in which a mucoid or resistant *Pa* culture was recorded in the CFFNPR since trial completion.

Clinical outcomes included antibiotic usage and rate of pulmonary exacerbations as defined by the physician and requiring home intravenous antibiotics or hospitalization. Exacerbations were counted as unique events if separated by at least 21 days. Antibiotic therapy received during the follow-up period was recorded at each clinical care episode. The forced expiratory volume in 1 second (FEV_1) was recorded among those old enough to perform spirometry and expressed as a percentage of predicted [15, 16].

Statistical Methods

Multivariable regression models included eradication status as the primary predictor, with a priori adjustment for age at completion of the trial, lifetime *Pa* history (never infected vs a history of *Pa* positivity >2 years prior to the start of the trial), and treatment received during the trial (cycled vs culture-based therapy). Further details can be found in the Supplementary Data.

RESULTS

Overview of the Study Cohort at Trial Completion

Of the 304 participants randomized into the EPIC trial, 249 (82%) completed the trial and continued in the EPIC observational study. Of these, 172 (69%) achieved sustained eradication of *Pa* during the trial ("sustained eradicators") and 77 (31%) failed to achieve sustained *Pa* eradication and had at least 1 recurrence of *Pa* within the last year of the trial ("nonsustained eradicators").

The mean age of the cohort at the end of the trial was 7.2 years, and average FEV_1% predicted was 97.7% (Table 1). No clinical characteristics significantly distinguished the sustained eradicators and nonsustained eradicators. The 55 trial participants not included in our study due to lack of follow-up data were younger than those in our cohort and had slightly lower FEV_1% predicted (Supplementary Table E1). Consistent with results from the trial [10], more participants on cycled therapy achieved sustained eradication (93/172 [54%]) compared with those on culture-based therapy (29/77 [38%]) (16% difference; 95% confidence interval [CI], 3%–29%); however, the majority of participants in the culture-based therapy group responded to subsequent antibiotic therapy so that the prevalence of positive *Pa* cultures at the end of the trial was the same between the cycled and culture-based groups (10% vs 11%, respectively).

Pa Recurrence Patterns After Completion of the Trial

The median follow-up time of the study cohort after completion of the study was 5.0 years (range, 0.3–6.6 years), with sustained eradicators having a slightly greater median follow-up time than nonsustained eradicators (5.1 vs 4.9 years, respectively). Overall, adherence to quarterly cultures during follow-up was high in this cohort, with 85% of 3995 total follow-up quarters having ≥1 culture result available; culture frequency was comparable between sustained eradicators and nonsustained eradicators (85% vs 84% of follow-up quarters with ≥1 culture result, respectively).

Over the follow-up period, 65 of 77 (84%) of the nonsustained eradicators vs 103 of 172 (60%) of the sustained eradicators experienced ≥1 *Pa* recurrence (Table 2). The median time to first *Pa* recurrence was 3.5 years among the sustained eradicators vs only 1 year among the nonsustained eradicators (a 58% reduction: hazard ratio [HR], 0.42; 95% CI, .3–.57). Treatment received during the trial was not significantly associated with *Pa* recurrence during follow-up.

Among those with a recurrence of *Pa*, 55% of the 103 sustained eradicators and 77% of the 65 nonsustained eradicators had a second recurrence of *Pa* during the follow-up period. Among those with a first *Pa* recurrence, the median time to second recurrence was 2.0 and 0.75 years for the sustained and nonsustained eradicators, respectively (HR, 0.55; 95% CI, .38–.81; Table 2).

Association Between Sustained Eradication and the Development of Chronic and Mucoid *Pa*

Whereas 56% of the 77 nonsustained eradicators developed chronic *Pa* infection during follow-up after a median of 3.25 years, only 23% of the 172 sustained eradicators developed chronic *Pa* infection (33% difference; 95% CI, 20%–45%). As shown in Table 3 and Figure 2*A*, sustained eradication during the trial was associated with a 74% reduced risk of development of chronic *Pa* infection (HR, 0.26; 95% CI, .17–.40), even after adjustment for potential confounders. Increasing age and

Table 1. Study Cohort Characteristics

Characteristic	Nonsustained Eradicator (n = 77)	Sustained Eradicator (n = 172)	Total (N = 249)	*P* Value
Sex				
Female	40 (51.9%)	86 (50.0%)	126 (50.6%)	.776
Age at trial completion, y				
Mean (SD)	7.6 (4.1)	7.0 (3.3)	7.2 (3.6)	.308
Age at trial completion				.079
<6 y	35 (45.5%)	79 (45.9%)	114 (45.8%)	
6 to <10 y	17 (22.1%)	57 (33.1%)	74 (29.7%)	
≥10 y	25 (32.5%)	36 (20.9%)	61 (24.5%)	
Race				.443
White	75 (97.4%)	163 (94.8%)	238 (95.6%)	
Hispanic	1 (1.3%)	1 (0.6%)	2 (0.8%)	
African American	. . .	5 (2.9%)	5 (2.0%)	
Unknown/other	1 (1.3%)	3 (1.7%)	4 (1.6%)	
Genotype				.928
F508 del homozygous	42 (54.5%)	88 (51.2%)	130 (52.2%)	
F508 del heterozygous	28 (36.4%)	64 (37.2%)	92 (36.9%)	
Other[a]	4 (5.2%)	12 (7.0%)	16 (6.4%)	
Unknown	3 (3.9%)	8 (4.7%)	11 (4.4%)	
FEV_1% predicted at trial completion				
No.	46	106	152	
Mean (SD)	98.0 (18.4)	97.6 (15.9)	97.7 (16.6)	.895
FEV_1% predicted distribution at trial completion				.708
<75%	3 (3.9%)	8 (4.7%)	11 (4.4%)	
75% to <100%	21 (27.3%)	55 (32.0%)	76 (30.5%)	
≥100%	22 (28.6%)	43 (25.0%)	65 (26.1%)	
Pa history prior to trial enrollment				.236
No lifetime history of *Pa* positivity	56 (72.7%)	112 (65.1%)	168 (67.5%)	
Lifetime history of *Pa* positivity	21 (27.3%)	60 (34.9%)	81 (32.5%)	
Treatment regimen received during the trial				.017
Cycled therapy	29 (37.7%)	93 (54.1%)	122 (49.0%)	
Culture-based therapy	48 (62.3%)	79 (45.9%)	127 (51.0%)	
Oral treatment (in addition to TIS) received during the trial				.394
Placebo	43 (55.8%)	86 (50.0%)	129 (51.8%)	
Ciprofloxacin	34 (44.2%)	86 (50.0%)	120 (48.2%)	

Data are presented as No. (%) unless otherwise specified.

Abbreviations: FEV_1, forced expiratory volume at 1 second; *Pa, Pseudomonas aeruginosa*; SD, standard deviation; TIS, tobramycin inhalation solution.

[a] Other refers to participants with 2 non-F508 del *CFTR* mutations.

lifetime history of *Pa* positivity were significantly associated with the risk of development of chronic *Pa* infection. Interestingly, use of cycled therapy during the trial was also associated with increased risk of the development of chronic *Pa* infection during the follow-up period.

Over the course of follow-up, 33% of the 77 nonsustained eradicators vs 17% of the sustained eradicators presented with mucoid *Pa* (16% difference, 95% CI, 4%–28%). Sustained eradication was associated with a 57% reduced risk of the appearance of mucoid *Pa* over the follow-up period (HR, 0.43; 95% CI, .25–.73; Figure 2*B*). In multivariable modeling, increased age and lifetime history of *Pa* positivity were also associated with increased risk of mucoid *Pa*, although use of cycled therapy during the trial was not (Table 3). Of the 168 participants with *Pa* recurrence, only 25 (15%) had at least 1 *Pa* isolate recorded as resistant to either aminoglycosides, quinolones, or β-lactams during the follow-up period, and these participants were comparably distributed by eradication status and use of cycled or culture-based therapy during the trial.

Table 2. Time to First and Second *Pseudomonas aeruginosa* Recurrence After Completion of the Clinical Trial, by Eradication Status

Recurrence	Nonsustained Eradicator (n = 77)	Sustained Eradicator (n = 172)	Overall (N = 249)	Difference or HR (95% CI)
First *Pa* recurrence				
Participants with at least 1 *Pa* recurrence, No. (%)	65 (84.4)	103 (59.9)	168 (67.5)	Difference, 24.5% (12.5%–34.4%)
Median time, y, to first recurrence (95% CI)	1.0 (.75–1.75)	3.5 (2.75–4.75)	2.75 (2.50–3.50)	HR, 0.42 (.30– .57)
Second *Pa* recurrence				
Participants with at least 2 *Pa* recurrences, No. (%)[a]	50 (76.9)	57 (55.3)	107 (63.7)	Difference, 21.6% (6.8%–34.5%)
Median time, y, to second recurrence since first recurrence (95% CI)	0.75 (.5–1.5)	2.00 (1.25–3.5)	1.50 (1.0–2.0)	HR, 0.55 (.38–.81)

Abbreviations: CI, confidence interval; HR, hazard ratio; *Pa*, *Pseudomonas aeruginosa*.

[a] Denominator is the number of subjects with at least 1 *Pa* recurrence.

Association Between Eradication and Long-term Clinical Outcomes

Overall, sustained eradicators had 50%–60% less usage of inhaled antibiotics and oral quinolones over the follow-up period compared with nonsustained eradicators, and comparable rates of macrolide usage (Supplementary Table E2). A total of 102 (59%) sustained eradicators vs 60 (78%) nonsustained eradicators recorded use of chronic inhaled antibiotics during the follow-up period, with median times to use of 3.61 and 0.79 years, respectively (HR, 0.52; 95% CI, .38–.72).

Of the 172 sustained eradicators, 48% had ≥1 pulmonary exacerbation during the follow-up period compared with 45% of the 77 nonsustained eradicators; event rates were comparable between sustained eradicators and nonsustained eradicators (rate ratio, 0.86; 95% CI, .54–1.34; Table 4). In multivariable regression modeling, female sex was significantly associated with exacerbation rate. Multivariable modeling did not include FEV_1% predicted due to a significant proportion of children too young for spirometry at the beginning of the follow-up period (38% of the cohort); however, among participants with spirometry, similar available findings were observed (Supplementary Table E3). Additional sensitivity analyses were performed to assess risk of exacerbations among nonsustained eradicators with more frequent recurrence of *Pa* during the trial, and although there was a trend toward an increased risk of exacerbations in this subcohort compared with the sustained eradicators, this result was not statistically significant (Supplementary Table E4).

Pulmonary function remained remarkably stable over the follow-up period, and the average rate of change in FEV_1% predicted in the study cohort was only −0.1% per year (95% CI, −.8% to .7%). After adjusting for potential confounders, the rate of change in FEV_1% predicted did not significantly differ between sustained eradicators (0.60% average increase per year; 95% CI, −2.18% to 3.39%) and nonsustained eradicators (−0.41% average decrease per year; 95% CI, −1% to .2%).

DISCUSSION

Our study represents the largest prospective study to date assessing long-term microbiologic and clinical outcomes among a cohort receiving standardized antipseudomonal therapy for newly acquired *Pa*. Prior studies have reported robust microbiologic response to early antipseudomonal therapy [3], and in the largest and longest eradication studies, EPIC [10] and ELITE [11], approximately 70% of children remained *Pa* culture negative in response to therapy for at least 18 to 27 months, respectively. Our study extends these results to show that for the majority of patients who are able to achieve sustained eradication as defined by *Pa* culture negativity throughout the final 12 months of the EPIC trial, the median time to subsequent *Pa* recurrence was an additional 3.5 years. Moreover, only 23% of those who achieved sustained eradication developed chronic infection over a median 5-year follow-up period, and only 17% developed mucoid *Pa*. Whereas prior studies have demonstrated a delay in chronic and mucoid *Pa* infection with early antipseudomonal therapy in comparison to no therapy [17–19], our study demonstrates a significantly increased risk of chronic and mucoid *Pa* among children who fail to achieve sustained eradication despite receiving antipseudomonal therapy. Although there is increased relative risk of these poor microbiologic outcomes among nonsustained eradicators, it is important to note that the absolute risk specifically for mucoid *Pa* remains low in this subcohort, with only 33% developing mucoid *Pa* during the median 5-year follow-up period.

In the original EPIC trial, slightly more participants who received cycled therapy achieved sustained eradication compared with those who received culture-based therapy. Our current study shows that those who received cycled therapy were at increased risk for the development of chronic infection. This suggests the potential that cycled antipseudomonal therapy may have been suppressing *Pa* culture positivity during the trial in

Table 3. Results From Univariate Unadjusted and Multivariable Adjusted Cox Proportional Hazards Models for the Association Between Eradication Status and Time to Chronic and Mucoid *Pseudomonas aeruginosa*

Variable	HR	95% CI	*P* Value
Time to chronic *Pa* (unadjusted)			
Nonsustained eradicator	. . .	. . .	. . .
Sustained eradicator	0.26	(.17–.40)	<.001
Time to chronic *Pa* (adjusted multivariable model)			
Nonsustained eradicator	. . .	. . .	. . .
Sustained eradicator	0.21	(.13–.33)	<.001
Age at trial completion			
<6 y	. . .	. . .	. . .
6 to <10 y	1.31	(.73–2.36)	.359
≥10 y	1.78	(1.00–3.19)	.052
Pa history prior to trial enrollment			
No lifetime history of *Pa* positivity	. . .	. . .	. . .
Lifetime history of *Pa* positivity	1.69	(1.01–2.82)	.046
Treatment regimen received during the trial			
Culture-based therapy	. . .	. . .	. . .
Cycled therapy	1.60	(1.02–2.53)	.042
Time to mucoid *Pa* (unadjusted)			
Nonsustained eradicator	. . .	. . .	. . .
Sustained eradicator	0.43	(.25–.73)	.002
Time to mucoid *Pa* (adjusted multivariable model)			
Nonsustained eradicator	. . .	. . .	. . .
Sustained eradicator	0.36	(.20–.63)	<.001
Age at trial completion			
<6 y	. . .	. . .	. . .
6 to <10 y	1.84	(.84–4.00)	.126
≥10 y	3.26	(1.52–6.98)	.002
Pa history prior to trial enrollment			
No lifetime history of *Pa* positivity	. . .	. . .	. . .
Lifetime history of *Pa* positivity	1.96	(1.06–3.63)	.032
Treatment regimen received during the trial			
Culture-based therapy	. . .	. . .	. . .
Cycled therapy	1.30	(.75–2.26)	.345

Abbreviations: CI, confidence interval; HR, hazard ratio; *Pa*, *Pseudomonas aeruginosa*.

some children, and because there was no evidence suggesting that these children remained on cycled therapy after the trial, that cessation of this therapy may have increased their risk for *Pa* recurrence. Thus, there remains no evidence for the benefit of cycled therapy over culture-based therapy with respect to long-term microbiologic outcomes.

The long-term health impact of new *Pa* acquisition remains unclear, particularly in the era of early antipseudomonal therapy. Those who failed to achieve sustained eradication had strikingly greater antibiotic usage than sustained eradicators, which may have confounded any comparisons between these groups. Overall, our study cohort remained relatively healthy, with approximately half of our cohort not experiencing a single pulmonary exacerbation requiring intravenous antibiotics or hospitalization during the median 5-year period, and the average rate of decline in FEV_1 in the cohort was only −0.1% per year. Importantly, there were no differences in clinical outcomes between those who achieved sustained eradication vs those who did not. There are several potential explanations for this finding. First, as evidenced in placebo-controlled clinical trials for established *Pa* infection [20, 21] that demonstrate improved clinical efficacy with administration of antipseudomonal therapy, it is possible that antipseudomonal therapy administered during early and intermittent infection is also having a positive impact on outcomes such as exacerbations and lung function that keep the nonsustained eradicators from declining in health despite recurrence of *Pa*. Second, contemporary cohorts such as the one in this study may be managing their *Pa* infection better because of advancing improvements in the management of CF, including better nutritional management and the adoption of several new therapies into the standard of care [21–25]. Last, as opposed to explanations focused on the host, it is possible that *Pa* itself is less pathogenic during initial and intermittent infection [9], and only has significant detrimental impact when chronic infection is established and upon increasing bacterial density in the airways.

Our findings of a lack of association between microbiologic response to early eradication therapy and clinical outcomes may also be explained by factors related to our study design. The median follow-up time of our cohort was 5 years; this may not have been a long enough period to assess outcomes related to the transition to chronic and mucoid *Pa*. Our study was also restricted to the definition of exacerbation recorded in the CFFNPR, representing more severe events requiring intravenous antibiotics or hospitalization. It is possible that there is a more measurable impact of sustained eradication on more mild exacerbations treated with oral or inhaled antibiotics. Although limited data collection was available in the follow-up study to quantify this, a suggestion that sustained eradication was associated with reduced frequency of more mild respiratory events is reflected in the significantly reduced rates of antibiotic usage among the sustained eradicators vs the nonsustained eradicators. Lack of sensitive outcome measures to capture decline in health in children with CF additionally remains a critical problem, and it is likely that FEV_1 is not a sensitive measure. Although one study has suggested that individuals who have cleared *Pa* after initial therapy have poorer lung function than those who had never been infected [8], recent studies have suggested that lung function does not deteriorate after new *Pa* acquisition in the presence of antipseudomonal treatment [5, 9].

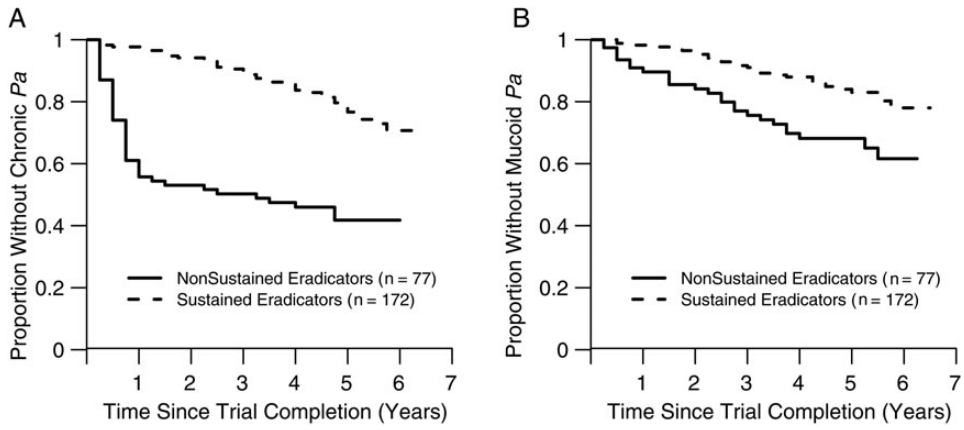

Figure 2. Kaplan–Meier plots of time to chronic *Pseudomonas aeruginosa* (*Pa*) infection (*A*) and time to mucoid *Pa* infection (*B*) after completion of the clinical trial, by eradication status.

Other studies have shown that the decline in lung function occurs only after acquisition of mucoid *Pa* [26].

There are several notable limitations to our study, including the restriction of our investigation to a cohort of children newly diagnosed with *Pa*. Additionally, there are no standardized definitions of eradication, and further work is needed to determine whether a duration of sustained eradication longer than assessed in this study is associated with better clinical outcomes. Our study relies heavily on accuracy of culture results, and although this was controlled during the clinical trial [12], this was not the case during the observational follow-up period. However, a recent audit was conducted that found excellent (98.9%) concurrence between microbiologic results recorded in the CFFNPR vs electronic medical records [27]. Second, it is possible that sampling approaches utilizing oropharyngeal swabs and sputum with traditional culture methods are not sufficiently sensitive to accurately characterize early stages of *Pa* infection in either the lower or upper airways, and thus are unable to detect underlying infection despite culture negativity for *Pa* [28, 29]. This approach remains the standard of care in the United States, however, and the prognostic ability of more sensitive monitoring of infection using serology to predict initial *Pa* infection, *Pa* recurrence, and treatment failure has not yet been demonstrated [30, 31].

In summary, children with sustained eradication after antipseudomonal therapy for newly acquired *Pa* have significantly better long-term microbiologic outcomes than those unable to achieve sustained eradication, including longer times to chronic and mucoid *Pa*. The lack of benefit of cycled therapy compared with culture-based therapy on long-term clinical and microbiologic outcomes continues to support current recommendations for use of culture-based therapy as an effective approach for management of early *Pa* infection [4]. The comparability of clinical outcomes between those who achieved sustained eradication vs those who did not suggests that the management of this entire cohort with the current standard of care has been successful in maintaining clinical stability with respect to lung

Table 4. Association Between Eradication Status and Rate of Physician-Defined Pulmonary Exacerbations Requiring Intravenous Antibiotics or Hospitalization During the Follow-up Period

	Rate Ratio	95% CI	*P* Value
Exacerbation rate (unadjusted)			
Nonsustained eradicator	. . .	. . .	. . .
Sustained eradicator	0.86	(.54–1.34)	.501
Exacerbation rate (adjusted multivariable model)			
Intercept	0.16	(.09–.28)	<.001
Nonsustained eradicator	. . .	. . .	. . .
Sustained eradicator	0.85	(.53–1.35)	.492
Sex			
Male	. . .	. . .	. . .
Female	1.82	(1.19–2.80)	.005
Age at trial completion			
<6 y	. . .	. . .	. . .
6 to <10 y	1.28	(.77–2.15)	.355
≥10 y	1.29	(.74–2.28)	.387
Pa history prior to trial enrollment			
No lifetime history of *Pa* positivity	. . .	. . .	. . .
Lifetime history of *Pa* positivity	1.38	(.86–2.22)	.206
Treatment regimen received during the trial			
Culture-based therapy	. . .	. . .	. . .
Cycled therapy	1.37	(.90–2.10)	.139

Abbreviations: CI, confidence interval; *Pa*, *Pseudomonas aeruginosa*.

function decline and pulmonary exacerbations requiring intravenous antibiotics. Despite this, those who fail to achieve sustained eradication are at greater risk of chronic and mucoid *Pa*, and although it is unclear how these key microbiologic endpoints impact subsequent clinical outcomes in an era of aggressive early antipseudomonal therapy, it is imperative that efforts continue to focus on improving eradication success through novel therapeutic approaches.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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