Published in final edited form as:

Pediatr Pulmonol. 2012 February ; 47(2): 125–134. doi:10.1002/ppul.21525.

Initial *Pseudomonas aeruginosa* Treatment Failure is Associated with Exacerbations in Cystic Fibrosis

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Abstract

Rationale—The risk of pulmonary exacerbation following *Pseudomonas aeruginosa* (*Pa*) acquisition in children with cystic fibrosis (CF) is unknown.

Objectives—To determine if failure of antibiotic therapy to eradicate *Pa* and frequency of *Pa* recurrence are associated with increased exacerbation risk.

Methods—The cohort included 282 children with CF who participated in the EPIC trial ages 1–12 with newly acquired *Pa*, defined as either a first lifetime *Pa* positive respiratory culture or positive after two years of negative cultures (past isolation of *Pa* but >2 years prior to the trial). All received antibiotics to promote initial eradication followed by 15 months of intermittent maintenance antibiotics. Quarterly cultures were used to define initial eradication success and subsequent number of *Pa* recurrences. A standardized symptom-based definition of exacerbation was utilized. Cox proportional hazards models were used to estimate exacerbation risk.

Results—Failure to initially eradicate *Pa* was associated with exacerbation risk (hazard ratio [HR]: 2.49, 95% confidence interval [CI] 1.26,4.93). In 245/282 with successful initial eradication during the trial, past isolation of *Pa* >2 years before the trial was the most significant predictor of exacerbation (HR 1.62, 95% CI 1.12,2.35). In 37/282 who failed initial eradication, persistent *Pa* during the maintenance phase (1 or more *Pa* recurrences after failure to initially eradicate) added even greater exacerbation risk (HR 4.13, 95% CI 1.28, 13.32).

Conclusions—Children with CF who fail to eradicate after initial antibiotic treatment are at higher risk of subsequent exacerbation, suggesting clinical benefit to successful early eradication of *Pa* infection.

Keywords

New acquisition; early intervention; eradication; clinical outcome

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Introduction

Pseudomonas aeruginosa (*Pa*) is the most common pathogen in cystic fibrosis (CF) airway disease, and after the establishment of chronic infection is associated with significant morbidity and mortality^{1–10}. Several studies have reported an association between new acquisition of *Pa* in childhood and poorer clinical outcomes after several years when compared to children who have not acquired *Pa*^{5–11}, suggesting a more gradual worsening of lung disease after *Pa* acquisition^{10,11}. Whether *Pa* acquisition has significant impact on shorter-term clinical outcomes remains an unanswered question.

The recently completed EPIC randomized clinical trial was designed to determine the optimal anti-pseudomonal treatment strategy in children with CF who recently acquired *Pa*, comparing the effectiveness of more aggressive versus less aggressive anti-pseudomonal treatment on both clinical and microbiologic outcomes¹². Specifically, the trial compared a cycled treatment regimen administered on a quarterly basis regardless of *Pa* culture results to a culture-based strategy in which treatment was administered on a quarterly basis only in response to *Pa* positive respiratory cultures. No differences in the primary clinical and microbiologic endpoints, time to pulmonary exacerbation and proportion of positive *Pa* cultures, were identified between treatment strategies over the 18 month study period¹³.

The richness of data from the EPIC trial provides a unique opportunity to investigate other clinically relevant questions such as the relationship between microbiologic outcomes and pulmonary exacerbation in a cohort of children with newly acquired *Pa*. In addition to frequent respiratory cultures and detailed microbiologic history since birth, a standardized, symptom-based definition of pulmonary exacerbation was utilized in the trial. Further, strict anti-pseudomonal treatment protocols for promoting initial *Pa* eradication and subsequent maintenance were followed, enabling a comprehensive evaluation of the association between newly acquired *Pa* and exacerbations in young children with CF in the presence of contemporary treatment approaches. Using the cohort of children enrolled in the EPIC clinical trial with recent new acquisition of *Pa* defined as either first documented lifetime *Pa* or *Pa* after at least two years of negative cultures, the objective of our study was to evaluate whether (1) past isolation of *Pa* (>2 years before enrollment), (2) failure to eradicate *Pa* after initial antibiotics received during the trial, and (3) frequency of *Pa* recurrence are associated with increased risk of a pulmonary exacerbation. Some of the results of this study were previously reported in abstract form¹⁴.

Materials and Methods

Eligibility

Children with CF ages 1–12 years with newly acquired *Pa* within six months of enrollment were eligible for the EPIC trial. Newly acquired *Pa* was defined as the first lifetime documented *Pa* positive culture or a *Pa* positive culture after a two-year absence of *Pa*. For children ages 12 to 15 months, at least one *Pa* positive culture since birth was required. Other eligibility criteria have been previously reported¹². All centers obtained institutional review board approval, and parents or guardians provided informed consent.

Study Design

During the first quarter of the study, all children received initial *Pa* eradication treatment consisting of 28–56 days of open label tobramycin inhalation solution (TIS, Novartis Pharmaceutical Corp), with half of the children randomly assigned to a concurrent 14-day course of oral ciprofloxacin (Bayer Healthcare AG) and half to oral placebo. Children were randomized to one of two maintenance treatment strategies administered over the five remaining quarters (15-months): (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. Treatment administered during the 15-month maintenance phase in both arms consisted of 28 days open-label TIS with either a concurrent 14-day course of oral ciprofloxacin or placebo as received during the first quarter (E-Figure 1 and E-Table 1, Online Supplement).

Pa culture status from birth was documented via medical records review. During the clinical trial, oropharyngeal cultures were obtained during follow-up at weeks 10, 22, 34, 46, 58, and 70 in addition to expectorated sputum cultures if available (<4% of children had sputum available at each visit). *Pa* culture results at week 10, obtained after antibiotic therapy received during the first quarter, were used to define initial eradication success or failure. All cultures were processed at the Center for CF Microbiology at Seattle Children's Hospital (Seattle, Washington) as previously described¹². Assessment for a pulmonary exacerbation was done at all scheduled study visits as well as acute illness visits. An *a priori*, established definition of pulmonary exacerbation was used for the determination of these events (E-Table 2, Online Supplement).

Statistical Analysis

Logistic regression was used to assess the association between baseline characteristics and failure to initially eradicate newly acquired *Pa* after antibiotics received in the first quarter. Cox proportional hazards regression was used to estimate associations of past isolation of *Pa*, failure to initially eradicate, and number of *Pa* recurrences after initial antibiotics with time to pulmonary exacerbation during the 15 month maintenance phase¹⁵. Number of *Pa* recurrences after initial antibiotic therapy was treated as a time dependent covariate throughout the maintenance phase. Potential confounders were assessed including age, gender, body mass index (BMI), genotype classification^{16–18}, and randomized treatment assignment. Odds and hazard ratios from the models were presented with 95% confidence intervals due to the exploratory nature of this study; *a priori* precision estimates for these analyses are provided in the Supplement (E-Table 3). Analyses were performed using R 2.11.1 (R Foundation for Statistical Computing, Austria).

Results

Characteristics of the Study Cohort by *Pa* Status after Initial Antibiotic Therapy

A total of 282/304 (93%) participants in the EPIC clinical trial were included in the study cohort, based on the availability of the initial eradication outcome at week 10. The 22 excluded children were similar to those included in the current analysis except for a slightly younger age and lower BMI (see E-Table 4, Online Supplement). There were 245/282 (87%) who achieved successful initial eradication, and 37/282 children (13%) who failed to eradicate recently acquired *Pa* at week 10. Baseline clinical and microbiologic characteristics are described separately in Table 1 for these two subgroups. No significant baseline clinical or microbiologic predictors of initial eradication success were identified.

Baseline and Initial Treatment Response Risk Factors for Exacerbation

A total of 44/282 (16%) participants met the *a priori* definition of pulmonary exacerbation and were treated with intravenous (IV) antibiotics, and 139/282 (49%) met the *a priori* definition of pulmonary exacerbation and were treated with antibiotics by any route of administration (oral, inhaled, or IV) during the 15-month maintenance phase. The risk of exacerbation in relation to baseline characteristics including past isolation of *Pa* (>2 years before enrollment), initial antibiotic treatment regimen, and failure to eradicate were evaluated. Table 2 displays the hazard ratios and corresponding confidence intervals quantifying the univariate associations between each potential risk factor and both

definitions of pulmonary exacerbation. Multivariable model development did not reveal significant interactions or differing results as compared to these univariate results.

Among the baseline characteristics evaluated, past isolation of *Pa* was significantly associated with an increased risk of an exacerbation. Children with past *Pa* as compared to those never colonized with *Pa* had significantly increased risk of an exacerbation treated with IV antibiotics (hazard ratio [HR] 2.12, 95% confidence interval [CI]: 1.17, 3.83) and antibiotics by any route of administration (HR 1.51, 95% CI 1.07, 2.12). No significant changes in these estimates of risk were identified after adjusting for age which by definition was highly correlated with past isolation of *Pa*. As seen in Table 2, age was not significantly associated with exacerbation risk. Figure 1 (panels a and b) displays the corresponding Kaplan-Meier plots for time to first exacerbation comparing those with first lifetime documented *Pa* to those with a past isolation of *Pa*.

Failure to eradicate *Pa* after initial antibiotics received during the trial was significantly associated with risk of exacerbation treated with IV antibiotics during the maintenance phase (HR 2.49, 95% CI 1.26, 4.93), and with an elevated but not significant risk of exacerbations treated with antibiotics by any route (HR 1.49, 95% CI 0.95, 2.36) (Table 2). Figure 1 (panels c and d) displays the corresponding Kaplan-Meier plots for time to first exacerbation comparing those who achieved initial eradication to those who failed. Of note, there were 5/37 (14%) of children who failed to initially eradicate at week 10 who were treated with inhaled or oral antibiotics for a pulmonary exacerbation at the time of failure to eradicate. As displayed in Figure 1 (d), these 5 children were responsible for most of the risk of exacerbations treated with antibiotics by any route among those who failed to initially eradicate *Pa*. As seen in Table 2, no significant differences between treatment regimens in the risk of exacerbation during the 15-month maintenance phase were found.

Association between *Pa* Recurrence during the Maintenance Phase and Risk of Exacerbation

Pa recurrence rates, defined by the number of *Pa* positive cultures from week 10 to the end of the 15-month maintenance phase, differed significantly between those who did and did not achieve initial eradication (Figure 2). A total of 65/245 (27%) children who achieved initial eradication at week 10 had at least one *Pa* positive culture during the maintenance phase, while 21/37 (57%) children who failed initial eradication had at least one additional *Pa* positive culture during the maintenance phase. Thus, the eradication outcome at Week 10 was significantly associated with subsequent *Pa* positivity over the remainder of the study (OR: 3.6, 95% CI: 1.8, 7.4, E-Figure 2).

Because of the observed difference in *Pa* recurrence rates between children who achieved initial eradication and those that failed, the association between the number of *Pa* recurrences and exacerbations was separately evaluated for each of these subgroups. Multivariable models were adjusted for past isolation of *Pa*, since this was found to be significantly associated with exacerbation risk. No significant interactions between the number of *Pa* recurrences and potential confounders, including treatment assignment, were identified. Table 3 displays the final model results for children who achieved initial eradication and those that failed.

Among those who achieved initial *Pa* eradication, past isolation of *Pa* was the most significant predictor of exacerbation risk. There was no significant difference in risk of an exacerbation comparing those who did and did not have recurrence of *Pa* during the maintenance phase. In contrast, among the children who failed initial eradication, past isolation of *Pa* was not significantly associated with risk of an exacerbation treated either with IV antibiotics or antibiotics by any route. Persistent *Pa*, defined as at least one

additional *Pa* positive culture after failure to eradicate, was significantly associated with an even greater risk of an exacerbation treated with antibiotics by any route but not with risk of an exacerbation treated with IV antibiotics.

Discussion

We have identified key microbiologic risk factors associated with increased risk of a pulmonary exacerbation after recent *Pa* acquisition treated with a standardized eradication regimen. Specifically, those children who failed to eradicate *Pa* with initial antibiotic treatment were at increased risk of a pulmonary exacerbation treated with IV antibiotics in the subsequent 15 months. While the majority of children included in our study successfully eradicated *Pa* after initial antibiotic therapy, the 13% that did not eradicate after initial antibiotics represent a vulnerable subgroup more likely to have frequent *Pa* recurrence and higher risk of a pulmonary exacerbation. Our eradication failure rates are comparable to those reported in previous studies^{19–23}, in particular to that observed in the recently completed ELITE trial for which approximately 10% of 120 children had a positive *Pa* culture or serologic response one month after completion of initial antibiotic therapy²⁴.

Our study complements prior studies by focusing on shorter term risk of exacerbation over 15 months rather than risk over a several year period^{5,6}. Our study evaluated two types of exacerbations, both those treated with IV antibiotics and those treated with antibiotics by any route of administration which enabled focus on the exacerbation definition independent of how the physician decided to treat. Our study found notable differences in risk factors for exacerbations between those with initial eradication success and failure. Past isolation of *Pa* was a risk factor for subsequent exacerbations only among those who achieved initial eradication. In contrast, *Pa* recurrence was a risk factor only among those who failed initial eradication. Those with persistent *Pa* during the study are perhaps best characterized as having emerging chronic infection as defined by respiratory cultures²⁵, and for whom it is no surprise has the greatest exacerbation risk. It will therefore be critical to further define the transition between early and chronic *Pa* infection in young children with CF, and whether failure to initially eradicate is indicative of this transition and thus the need for more effective treatment approaches.

The exploratory nature of our study implies important key limitations that must be considered. The study cohort was confined to children enrolled in the EPIC clinical trial and thus our results may not be generalizable to the population of children with CF and newly acquired *Pa*. The average FEV₁% predicted in the older children at baseline was 96% with no observed changes over the course of the study¹³, and thus represented a group with relatively normal lung function. Thus, the duration of this study might not have been sufficient to investigate the relationship between exacerbation events and decline in lung function. Secondly, we must be careful to remember that associations may not be causal. For instance, it may be that children who fail to eradicate are subject to more rigorous symptom surveillance and thus there is an indication bias for the diagnosis of a pulmonary exacerbation. It should be noted however that since pulmonary exacerbations comprised the primary efficacy endpoint in the clinical trial, a rigorous surveillance was promoted among all children enrolled in the trial regardless of treatment group and microbiologic status. In addition, it is important to note that past isolation of *Pa* and failure to eradicate may simply be markers for unmeasured characteristics which are more directly and causally related to exacerbation risk, for example structural airway damage. Lastly, the precision for which we can estimate associations in this study, particularly among those who failed to initially eradicate *Pa*, is limited by both the size of the cohort and incidence of exacerbation events. Thus, there may be important associations for which there was insufficient data to deem statistically and clinically significant. Despite these limitations, the results of our study

provide a working hypothesis for the relative impact of lifetime history of *Pa* positivity, failure to initially eradicate *Pa*, and *Pa* recurrence on the risk of a pulmonary exacerbation.

In summary, clinical and microbiologic data acquired during the EPIC clinical trial has provided the opportunity to investigate the association between newly acquired *Pa*, treatment response, and risk of pulmonary exacerbation in young children with CF. This study identified a small but clinically important group of children with CF who fail to achieve initial *Pa* eradication and who are at higher risk of exacerbation, and suggests clinical benefit among those with successful initial eradication. Ongoing studies utilizing banked sera and *Pa* isolates collected in the EPIC clinical trial will provide important complementary data for determining whether there are bacterial phenotypic characteristics or serologic markers that can further depict the association between early *Pa* infection patterns and clinical outcome in children with CF. These findings may ultimately help to identify high risk groups that will benefit from alternative antibiotic regimens targeted towards *Pa* so that in the future, all children with CF will successfully eradicate this bacterial pathogen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Special thanks to families of CF children who participated in the study and whose dedication to research made the trial possible.

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Cystic Fibrosis Foundation Therapeutics: Robert J. Beall, Preston W. Campbell III, Bruce C. Marshall.

CF Services: Robin Carter, Wayne Gabbert, Edmond Grantham, Asif Khan, Daniel Klein, Kevin Smith, Jim Stone.

CF Services Pharmacy: Michael Arnold, Erica Crilly, Paul Jennings, Kwei Leong, Mike Sullivan, Brian Van Etten.

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Platzker; RC: Ricardo Ortego; Children's Hospital of Michigan Wayne State University, Detroit, MI – SI: Ibrahim Abdulhamid and Debbie Toder; RC: Catherine Van Wagnen; Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA – SI: David Orenstein; RC: Judy Fulton and Sandy Hurban; Children's Hospital of Wisconsin/Medical College of Wisconsin, Milwaukee, WI – SI: William Gershan; RC: Tami Miller; Children's Hospitals and Clinics of Minnesota, Minneapolis, MN – SI: John McNamara and Michael Pryor; RC: Sandy Landvik and Mary Sachs; Children's Memorial Medical Center, Chicago, IL – SI: Adrienne Prestridge; RC: Stacy VandenBranden; Children's Mercy Hospital, Kansas City, MO – SI: Philip Black; RC: Lora Bear, Mary Matzedar and Karie Robinson; Cook Children's Health Care System, Fort Worth, TX – SI: Maynard C. Dyson and Karen D. Schultz; RC: Sara Scott; Dartmouth Hitchcock Medical Center, Lebanon, NH – SI: H. 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Royce; The Johns Hopkins Medical Institutions, Baltimore, MD – SI: Peter J. Mogayzel, Jr. and Pamela L. Zeitlin; RC: Karen A. Callahan and Carolyn G. Chapman; The PennState Milton S. Hershey Medical Center, Hershey, PA – SI: Gavin R. Graff and Michael S. Schwartz; RC: Lisa M. Allwein and Diane M. Kitch; The University of Alabama at Birmingham, Birmingham, AL – SI: Hector H. Gutierrez; RC: Lacreia Britton, Valerie Eubanks Tarn and Gina Sabbatini; University of California, San Francisco, San Francisco, CA – SI: Dennis W. Nielson; RC: Diem Tran; University of Iowa, Iowa City, IA – SI: Richard C. Ahrens; RC: Jean Frauenholtz, Liz Huey and Mary Teresi; University of Kentucky College of Medicine, Lexington, KY – SI: Michael I. Anstead and Jamshed F. Kanga; RC: Catherine Dudderar and Barbara Owsley; University of Massachusetts Memorial Health Care, Worcester, MA – SI: Brian P. O'Sullivan; RC: Dawn Baker; University of Michigan, Ann Arbor, MI – SI: Samya Z. 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Rock; RC: Linda Makholm; Vanderbilt Children's Hospital, Nashville, TN – SI: Christopher Harris and Elizabeth Perkett; RC: Alice Bray; Vermont Children's Hospital at Fletcher Allen Health Care, Burlington, VT – SI: Thomas Lahiri; RC: Sandra Diehl and Emily Keller.

Financial support: The research for this article was supported in part by the Cystic Fibrosis Foundation grant number EPIC0K0, the National Heart Lung and Blood Institute (NHLBI) and National Institute for Digestive Disorders and Kidney (NIDDK) grant number U01-HL080310, and the National Center for Research Resources (NCRR) grant numbers UL1-RR025014-03, 1UL1-RR025744, 1UL1-RR025780, UL1-RR025005, UL1-RR0024979, UL1-RR025747, UL1-RR025011, 1UL-RR024975, M01-RR02172. Study drugs and devices for the clinical trial were supplied free of charges by Novartis Pharmaceutical Corp. (tobramycin inhalation solution) and Bayer Healthcare AG (oral ciprofloxacin and oral placebo), compressors and nebulizers were provided by PARI Respiratory Equipment Inc. The industry sponsors had no role in the analysis, interpretation or writing of the manuscript.

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Figure 1.

Kaplan Meier plot of time to first pulmonary exacerbation treated with either IV antibiotics (a and c) or antibiotics by any route of administration (b and d), comparing those with newly acquired *Pa* who entered the trial with no history of *Pa* colonization versus those who entered with past isolation of *Pa* (>2 years prior to enrollment) (a and b), and those who achieved successful initial eradication at week 10 to those who failed to achieve successful initial eradication (c and d).

Figure 2. Distribution of the number of *Pa* positive cultures from week 10 through the end of the 15-month maintenance phase for subgroups defined by initial eradication success at week 10.

Table 1

Baseline characteristics and initial antibiotic therapy received for newly acquired *Pa* comparing those who achieved initial eradication of *Pa* at week 10 and those who failed to eradicate at week 10. Odds ratios are provided from univariate logistic regression models for the odds of failing to eradicate at week 10.

	<i>Pa</i> + at Week 10 (N=37)	<i>Pa</i> - at Week 10 (N=245)	Odds Ratio (95% CI)
Baseline Characteristics			
Female, n (%)	16 (43)	129 (53)	0.69 0.34,1.38
Age in years, mean (SD)	5.8 (3.62)	5.8 (3.54)	1.00 0.91,1.10
FEV ₁ % predicted [‡] , mean (SD)	101.9 (19.04)	95.6 (16.44)	1.02 0.99, 1.06
BMI (kg/m ²), mean (SD)	16.5 (1.79)	16.7 (1.84)	0.95 0.78,1.16
Genotype, n (%)			
ΔF508 heterozygous	19 (51)	89 (36)	-
ΔF508 homozygous	16 (43)	124 (51)	0.60 0.29,1.24
Other	2 (5)	20 (8)	0.47 0.10,2.18
Unknown	0 (0)	12 (5)	NA
CFTR genotype class [*] , n (%)			
A	25 (68)	188 (77)	-
B	6 (16)	19 (8)	2.37 0.87,6.51
Unclassified	6 (16)	26 (11)	1.74 0.65,4.63
Unknown	0 (0)	12 (5)	NA
Past isolation of <i>Pa</i> [‡] , n (%)	13 (35)	81 (33)	1.10 0.53,2.27
Total number of <i>Pa</i> + cultures since birth, n (%)			
1	24 (65)	164 (67)	-
2	6 (16)	45 (18)	0.91 0.35,2.36
3 or more	7 (19)	36 (15)	1.33 0.53,3.32
<i>S. aureus</i> at baseline [‡] , n (%)	18 (49)	142 (60)	0.63 0.32,1.27
<i>S. maltophilia</i> at baseline [‡] , n (%)	1 (3)	9 (4)	0.70 0.09,5.72
Initial Antibiotic Therapy for New Onset <i>Pa</i>			
Antibiotics received during the trial, n (%)			
TIS with placebo	17 (46)	128 (52)	-

	<i>Pa</i> + at Week 10 (N=37)	<i>Pa</i> - at Week 10 (N=245)	Odds Ratio (95% CI)
TIS with ciprofloxacin	20 (54)	117 (48)	1.29 0.64,2.57

TIS= Tobramycin inhalation solution; SD=Standard deviation; BMI = Body mass index; CI= Confidence Interval; *Pa* = *P. aeruginosa*; *S. aureus* = *Staphylococcus aureus*; *S. maltophilia* = *Stenotrophomonas maltophilia*.

* Cystic fibrosis transmembrane conductance regulator (CFTR) mutations were classified based on functional class. Genotypes with both CFTR mutations in functional classes I, II, or III (severely reduced CFTR function) were considered class A; genotypes with one or both mutant alleles in class IV or class V (some residual CFTR function) were considered class B. Genotypes in which a functional class could not be assigned for one or both alleles were considered unclassified¹⁵⁻¹⁷.

[†] The positive *Pa* culture used for eligibility into the trial was newly acquired after a 2 year history of negative *Pa* cultures, and there was at least one *Pa* positive culture prior to this window since birth.

[‡] Baseline spirometry results were available for 17/37 older children who were *Pa*+ at week 10 and able to perform spirometry and 134/245 *Pa*- children. Baseline microbiology results were available for 237/245 children who were *Pa* - at week 10.

Table 2

Hazard ratios and 95% confidence intervals from univariate Cox proportional hazards models used to assess whether select baseline characteristics and treatment were associated with the risk of (a) pulmonary exacerbation treated with IV antibiotics, and (b) pulmonary exacerbation treated with antibiotics by any route of administration.

Baseline Characteristics	(a) PE Treated with IV Antibiotics		(b) PE Treated with any Antibiotics	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Female	1.32	0.73,2.40	1.03	0.74,1.44
Age, yr	1.02	0.94,1.10	1.01	0.96,1.06
FEV ₁ % Predicted	0.98	0.96, 1.00	0.99	0.98, 1.00
BMI (kg/m ²)	0.95	0.80,1.13	0.97	0.89,1.07
Genotype				
ΔF508 heterozygous	-	-	-	-
ΔF508 homozygous	1.37	0.70,2.70	1.33	0.92,1.92
Other	1.48	0.48,4.53	1.36	0.72,2.56
CFTR genotype class [*]				
A	-	-	-	-
B	1.14	0.40,3.22	0.97	0.53,1.77
Unclassified	1.07	0.41,2.73	1.12	0.67,1.87
Past isolation of <i>Pa</i>	2.12	1.17,3.83	1.51	1.07,2.12
Total number of <i>Pa</i> + cultures since birth				
1	-	-	-	-
2	3.07	1.61,5.84	1.77	1.18,2.64
3 or more	1.16	0.47,2.87	1.23	0.77,1.97
<i>S. aureus</i> + at baseline	0.79	0.44,1.45	0.89	0.63,1.24

	(a) PE Treated with IV Antibiotics		(b) PE Treated with any Antibiotics	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
<i>S. maltophilia</i> + at baseline	NA [†]	NA [†]	1.67	0.74,3.80
Failure to Eradicate <i>Pa</i> after Initial Antibiotic Therapy				
<i>Pa</i> positive at Week 10	2.49	1.26,4.93	1.49	0.95,2.36
Treatment after Initial Antibiotic Therapy[‡]				
Culture-based TIS with placebo	-	-	-	-
Culture-based TIS with ciprofloxacin	1.18	0.52,2.68	1.51	0.96,2.39
Cycled TIS with placebo	0.61	0.24,1.59	0.85	0.52,1.40
Cycled TIS with ciprofloxacin	1.32	0.60,2.91	1.00	0.62,1.62

PE= pulmonary exacerbation; TIS= Tobramycin inhalation solution; SD=standard deviation; BMI = Body mass index; CI= Confidence interval; *Pa* = *P. aeruginosa*; *S. aureus* = *Staphylococcus aureus*; *S. maltophilia* = *Stenotrophomonas maltophilia*

* Class A, both mutations in functional class I, II, or III; class B, one or both mutations in functional class IV or V; Unclassified, one or both mutations could not be assigned to a functional class.

[†] 10 patients had *S. maltophilia* at baseline and none had exacerbations treated with IV antibiotics.

[‡] There were 71 children in the culture-based TIS with placebo group, 66 children in the culture-based TIS with ciprofloxacin group, 74 children in the cycled TIS with placebo group, and 71 children in the cycled TIS with ciprofloxacin group.

Table 3

Hazard ratios and 95% confidence intervals from multivariable, time dependent Cox proportional hazards models used to assess whether *Pa* recurrence after initial antibiotic therapy is associated with the risk of (a) pulmonary exacerbation treated with IV antibiotics, and (b) pulmonary exacerbation treated with antibiotics by any route of administration. Models were adjusted for past isolation of *Pa* and generated separately for the cohort who achieved successful eradication at week 10 and those who failed to achieve successful eradication at week 10. No significant interactions were identified.

	(a) PE Treated with IV Antibiotics		(b) PE Treated with any Antibiotics	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Results for Cohort who Achieved Initial <i>Pa</i> Eradication (n=245)				
Past isolation of <i>Pa</i>	2.62	1.31,5.22	1.62	1.12,2.35
Number of <i>Pa</i> recurrences after initial antibiotic therapy				
0	-	-	-	-
1 or more	1.19	0.45,3.20	1.23	0.70,2.16
Results for Cohort who Failed to Achieve Initial <i>Pa</i> Eradication (n=37)				
Past isolation of <i>Pa</i>	0.89	0.26,3.09	0.83	0.34,2.01
Number of <i>Pa</i> recurrences after initial antibiotic therapy				
1	-	-	-	-
2 or more	2.66	0.72,9.87	4.13	1.28,13.32

PE= pulmonary exacerbation; *Pa* = *P. aeruginosa*; CI= confidence interval.