Published in final edited form as:

Pediatr Pulmonol. 2015 March ; 50(3): 236–243. doi:10.1002/ppul.23056.

Pulmonary exacerbations and parent-reported outcomes in children < 6 years with cystic fibrosis

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Summary

Pulmonary exacerbations (PEs) are used as clinical endpoints in infants and preschool children with cystic fibrosis (CF); however, their characteristics and impact in this age range are poorly understood. We used data from the Infant Study of Inhaled Saline, a multicenter trial of inhaled hypertonic versus isotonic saline, to describe PEs in children with CF <6 years and evaluate associations between PEs and parent-reported outcomes assessed by a weekly parent questionnaire (10 items) and 3 scales of the Cystic Fibrosis Questionnaire-Revised (CFQ-R), and other participant characteristics. There were 659 PEs among 253 of the 321 ISIS participants (mean age 2.3 years) during 287 participant-years follow-up. Of the 659 PEs, 636 (97%) were treated with oral and 45 (7%) with IV antibiotics (not mutually exclusive). Among 222 participants with PEs who had completed parent questionnaires during a PE and at baseline, 9 of the 10 symptoms were each present in a statistically significantly higher proportion of participants during a PE than at baseline. Lower (worse) baseline Respiratory Symptom and Physical Functioning CFQ-R scores were significantly associated with higher PE rate: rate ratio 1.08 (95%CI: 1.02, 1.14) and 1.21 (1.07, 1.36) per 10 point lower score in respective scale. A higher PE rate was also significantly associated with worse CFQ-R Respiratory Symptom and Physical Functioning scores at the end of the study, adjusted for baseline scores. Though most PEs did not require IV antibiotics, PEs appeared to have a negative impact on parent-reported health outcomes in infants and preschoolers with CF.

Keywords

Pulmonary exacerbations; respiratory symptoms; Cystic Fibrosis Questionnaire-Revised; infants

Introduction

Cystic fibrosis (CF) lung disease is characterized by episodic increases in respiratory symptoms, such as cough and sputum production, occasionally accompanied by systemic symptoms, such as fatigue or anorexia, termed “pulmonary exacerbations (PEs)”^{1,2}. In school-age and adult patients with CF, PEs have been shown to have a significant impact on lung function³, mortality⁴⁻⁵, health-related quality of life⁶⁻⁷ and health care expenditures⁸, and have served as a key clinical trial endpoint⁹⁻¹⁰.

The evidence is now clear that CF lung disease begins early, often in infancy and before the onset of symptoms¹¹. The recent widespread adoption of newborn screening allows for clinical trials of therapies in infants and preschoolers to delay or prevent irreversible lung disease. Although PEs are beginning to be used as clinical trial endpoints in children <6 years of age¹²⁻¹⁴, little is known about PEs in this very young age range and a standardized definition is lacking. To develop PEs as a clinically meaningful endpoint for children <6 years of age, the characteristics, predictors and outcomes of PEs in this age range must be better understood. In addition, the association of PEs, which are determined by clinicians based on the decision to treat with antibiotics, with parent-reported signs and symptoms needs to be established.

The Infant Study of Inhaled Saline (ISIS) trial¹⁴ was a multicenter randomized controlled trial of inhaled hypertonic versus isotonic saline for 48 weeks in children with CF 4 to 60 months of age; PEs were the primary endpoint. While there was no difference in the rate of PEs between the two treatment arms, data from this trial provide an important opportunity to evaluate PEs and their relationship to parent-reported outcomes in young children. Therefore, our aims were to describe the characteristics of PEs in children with CF <6 years of age and to evaluate the associations between PEs and parent-reported outcomes, as well as other patient characteristics.

Materials and Methods

Design and Participants

Participants were from the Infant Study of Inhaled Saline (ISIS), which has previously been described in detail¹⁴. Briefly, ISIS was a 30-center, randomized, double-blind, controlled clinical trial of 7% hypertonic saline (active treatment) versus 0.9% isotonic saline (control), inhaled twice daily for 48 weeks among children with an established diagnosis of CF who were 4 to 60 months of age at enrollment.

Pulmonary exacerbations (PE)

A pulmonary exacerbation (PE) was defined as treatment with oral, inhaled, or intravenous antibiotics for 1 or more pre-specified signs and symptoms¹⁴ within a period of 3 days prior

to the antibiotic start date through the antibiotic stop date. Route types (oral, inhaled, IV) were not mutually exclusive since multiple antibiotics might have been recorded for the same exacerbation. The pre-specified signs and symptoms were: 1) increased cough; 2) increased chest congestion or change in sputum; 3) new or increased adventitious sounds on lung exam; 4) worked harder than usual to breathe during physical activity; 5) increased work of breathing or respiratory rate; 6) new lobar infiltrate(s) or atelectasis on chest radiograph; 7) weight loss $\geq 5\%$ of body weight or decrease across 1 major percentile in weight percentile for age in past 6 months; 8) oxygen saturation $<90\%$ on room air *or* $\geq 5\%$ decline from previous baseline; and 9) hemoptysis. Each time an antibiotic was prescribed during the study, clinicians answered “yes”, “no”, or “not available” for each sign or symptom. As in-person assessments for respiratory illnesses were not required per protocol, questions regarding these signs and symptoms were not necessarily answered at the time of the event.

Parent-reported signs and symptoms: Weekly parent questionnaire and CFQ-R

Parents completed a questionnaire (10 items) about their child's symptoms on a weekly basis, either electronically or on paper. Three scales of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) for Parents/Caregivers of Children Ages 3-6¹⁵ were administered at each study visit (baseline, week 12, week 24, week 36 and week 48): Respiratory Symptoms, Treatment Burden and Physical Functioning. (The Physical Functioning scale was only completed for participants age >3 years, since these items are not appropriate for infants and toddlers). Scaled scores range from 0 to 100, with higher values indicating better health.

Statistical analysis

The percentage of each PE-related sign or symptom was summarized for all PEs and by antibiotic type (oral, inhaled, IV). The presence of the sign or symptom was based on the clinician report at the time of first prescription of that antibiotic type.

Among participants with PEs, the number of participants with each symptom and also with at least one symptom on the weekly parent questionnaire was summarized 1) during the first PE with a completed questionnaire, and 2) at baseline or the first time not during a PE with a completed questionnaire. We evaluated the statistical significance of the difference in percentages of each symptom between baseline and exacerbation by McNemar's test. We also evaluated the statistical significance of the difference in mean number of symptoms from the weekly parent questionnaire at baseline and during PE with the paired t-test, and the difference in the distributions of the number of symptoms with the Wilcoxon signed rank test.

Four of the questions on the weekly parent questionnaire were similar to the signs and symptoms of a PE as assessed by the clinician. For each of these, we computed the concordance, i.e., the number of responses during a PE in which the parent and clinician responses were the same (both “yes”, or both “no”) divided by the total number of responses during a PE. If the clinician reported that the sign or symptom was “not available” (e.g., consolidation on chest radiograph), the response was treated as “no” for the primary analysis.

The association between the weekly parent questionnaire (number of 10 symptoms reported as present) and the CFQ-R Respiratory Symptom score was evaluated by simple linear regression. For each participant, the first set of complete matching questionnaires (at baseline, week 12, week 24, week 36, or week 48) was used for analysis.

We evaluated the association between PEs and baseline participant characteristics (baseline CFQ-R scores, age, gender, height and weight percentiles, genotype, and presence of *Pseudomonas aeruginosa*) using Poisson regression with log of observation time as an offset term to account for different follow-up times among participants. We also evaluated the association between PE rate and final CFQ-R scores using linear regression with PE rate (number of PEs divided by participant observation time) as the predictor of interest, with and without adjustment for baseline CFQ-R scores. For the models, CFQ-R scores were transformed into negative values to aid interpretation. Analyses were performed in STATA 12.0, and p-values less than 0.05 were considered statistically significant.

Results

A total of 321 participants at 30 sites were enrolled between April 2009 and October 2010; baseline participant characteristics are summarized in Table 1. The mean age at enrollment was 2.3 years (standard deviation: 1.5; range 0.3, 5), 55% were male, and 94% were non-Hispanic white.

There were a total of 659 PEs among 253 (78%) of the 321 participants during 287 participant-years of follow-up. Mean pulmonary exacerbation rate (events/person-year) among all participants was 2.3 (95% CI, 2.0, 2.5). Of the 659 PEs, 636 (97%) from 250 participants were treated with oral antibiotics, 50 (8%) from 39 participants with inhaled and 45 (7%) from 38 participants with IV antibiotics. The most commonly reported PE-related sign or symptom was increased cough, present in 640 (97%) of the PEs (Table 2). Increased chest congestion or change in sputum, present in 202 (31%) of the PEs, was the second most common sign or symptom. All other signs/symptoms were less frequent; hemoptysis was reported only once. Among the 659 PEs, 419 (64%) were associated with only one reported sign or symptom. Cough was the only reported symptom in 406 (62%) of the PEs. Two signs or symptoms were reported in 145 (22%), and three or more in 95 (14%). The presence of multiple reported signs/symptoms was more frequent for the 49 PEs requiring IV antibiotics, 22 (49%) of which had three or more reported associated signs or symptoms.

Figure 1 shows the rate of PEs by calendar month and year during the study. In general, rates were highest in the fall and winter months. Results are similar when PE rates were summarized by month (where observation time was relatively constant), instead of month and year (e.g. any June instead of June '09, June '10, June '11).

Among the 253 participants with PEs, 222 participants had completed weekly parent questionnaires both during the week of onset of PE and at baseline or another time not during a PE. Parents did report symptoms at baseline, however 9 of the 10 symptoms (all except cranky/fussy) were each reported in a significantly higher proportion of participants during a PE (Table 3). For example, "cough at times other than 10 minutes within saline

treatment” was reported in 33% of participants at baseline and 68% during a PE (difference=35%, $p<0.0001$). At least 1 of the 10 symptoms was reported in 61% of participants at baseline and 78% during a PE (difference=17%, $p=0.0001$). The mean number of reported symptoms among participants was 1.4 at baseline and 2.9 during a PE (difference = 1.5, $p<0.0001$).

The concordance between clinician-reported symptoms of a PE and parent-reported symptoms from the weekly parent questionnaire (completed during the week of PE onset) ranged from 55% to 81% (Table 4). For example, the concordance between “coughing at times other than 10 minutes within saline treatment” as reported by the parent and “increased cough” as reported by the clinician was 70%.

The weekly parent questionnaire at baseline (number of 10 symptoms which were reported as present) was statistically significantly associated with the CFQ-R Respiratory Symptom score at baseline. One more reported symptom on the weekly parent questionnaire was associated with a 2.3-point (95% CI: 1.3, 3.2; $p<0.0001$) lower (worse) CFQ-R Respiratory Symptom score on average, among 302 participants with both a completed parent questionnaire and CFQ-R Respiratory Symptom score at the same time during the study.

The association between PEs and CFQ-R Scale scores is summarized in Table 5. Lower (worse) Respiratory Symptom and Physical Functioning scores at baseline predicted a significantly higher PE rate during the study period. For example, a 10-point lower (worse) baseline Respiratory Symptom score was associated with a 1.08-fold higher PE rate (95% CI: 1.02, 1.14; $p=0.005$). In addition, a higher PE rate was associated with significantly lower (worse) Respiratory Symptom and Physical Functioning scores at the end of the study, even after adjustment for baseline CFQ-R scores. For example, given the baseline score, 1 additional PE per year was associated with a 1.45 (95% CI 0.58, 2.33) lower (worse) Respiratory Symptom score at the end of study ($p=0.001$).

No significant associations between PEs and Treatment Burden scores were found. In addition, no significant associations were detected between PE rate and baseline age, gender, weight percentile, height percentile, CF genotype, or presence of *Pseudomonas aeruginosa* (Table 6).

Discussion

In this study of PEs in children with CF <6 years of age, we found that exacerbations were common (occurring in 78% of participants in a 48-week period). Cough was the primary symptom, present in 97% of all exacerbations and indeed the only clinician-reported symptom in the majority. Only 7% of PEs required IV antibiotics; these exacerbations had more reported signs and symptoms than those treated with oral antibiotics. Exacerbation rates displayed a seasonal pattern, with higher rates in the fall and winter, presumably during the respiratory viral season. Even though only one sign or symptom was reported by the clinician for most PEs, we detected significant worsening of most parent-reported symptoms during a PE. Importantly, we also found significant associations between PEs and 2 scales of the CFQ-R. Lower (worse) baseline CFQ-R Respiratory Symptom and Physical Functioning

scores each predicted a significantly higher PE rate, and a higher PE rate in turn predicted worse Respiratory Symptom and Physical Functioning scores at the end of the study.

Our results complement and expand on those of the two prior studies of PEs in children with CF <6 years of age¹⁶⁻¹⁷. Rabin and colleagues¹⁶ found that new crackles, increased cough, decline in weight-for-age percentile and increased sputum were the 4 clinical characteristics most associated with a PE in patients <6 years of age. Similar to our results, they found that treatment with IV antibiotics was more likely as the number of signs/symptoms increased. More recently, Byrnes, et al¹⁷ reported on PEs in the cohort of children enrolled in the Australasian CF Bronchoalveolar Lavage (ACFBAL) trial and the impact of these exacerbations on lung function and structure at age 5. They defined exacerbations as “any change in respiratory symptoms from baseline.” Nonetheless, the signs and symptoms of a PE in their cohort were very similar to ours. Importantly, they found that early exacerbations were clearly associated with long term sequelae: a higher exacerbation rate during the first 2 years of life was associated with lower lung function at age 5, and ever having had an exacerbation requiring hospitalization was associated with a 2.7-fold increased risk of bronchiectasis on chest CT at age 5. We add to this literature by demonstrating a significant association between worsening of parent-reported symptoms and PEs, concordance between clinician and parent-reported symptoms of PEs, and significant associations between CFQ-R scores and PE rate.

In older patients with CF with more established disease, the important sequelae of exacerbations are well-established: loss of lung function³, increased short-term mortality⁴⁻⁵, reduced quality of life⁶⁻⁷ and significant health care expenditures⁸. In young children, exacerbations are milder and generally treated with oral antibiotics. Additionally, they are most likely to be virally triggered, as evidenced by their seasonal pattern. Thus, a reasonable question is whether they matter? The emerging results, from the work of Byrnes and colleagues¹⁷ as well as ours, indicate that they do have an impact. They are associated with decreased health-related quality of life, loss of lung function and, if requiring hospitalization, a greater odds of bronchiectasis at age 5.

Given that there is no standardized definition of a PE, particularly in young children, our definition was adapted from that employed in two prior clinical trials conducted in children with mild lung disease uninfected with *Pseudomonas*, the first enrolling children with CF <12 years of age¹² and the second enrolling children 6 to 18 years of age¹⁸⁻¹⁹. The frequency of signs and symptoms of an exacerbation in our younger cohort was similar to that reported in these two older cohorts. In all three cohorts, the prevalence of hemoptysis and weight loss > 5% of body weight was very low, suggesting these two characteristics could probably be eliminated from the PE diagnostic criteria in young children or those with mild disease.

Our study has several strengths. Participants were from 30 clinical centers in the United States and Canada. While signs and symptoms associated with exacerbations were captured in a standardized manner, the decision to treat was entirely at the discretion of the clinician, allowing us to evaluate the wide range of exacerbations as determined by treating clinicians. The parent questionnaire was completed weekly, making it possible to compare symptoms

during sick and well periods. Our study also had limitations. PEs were based on a clinical decision to treat with antibiotics and the presence of one or more pre-specified symptoms. Thus, children who had one or more pre-specified symptoms but were not treated with antibiotics were not considered to have a PE in this study. Pre-specified signs or symptoms which were reported as “not available” were treated as “no” for our primary analysis. It is possible that some of these signs or symptoms were present, but unknown to the clinician; however, our primary conclusions remain the same regardless of how the “not available” responses are treated. This study was performed within the context of a clinical trial, which could affect generalizability. It was an observational study of the relationship between PEs and parent-reported outcomes, and causation cannot be assessed here. The minimum clinically important difference (MCID) for the CFQ-R scores are not known for children with CF <6 years of age, although the MCID for the CFQ-R respiratory score among older patients with stable respiratory symptoms has been reported by Quittner et al.²⁰ to be 4.0 points. There was some missing data; of the 253 participants with a PE, 222 (88%) had weekly parent questionnaires both during a PE and at baseline (or not during a PE). However, when we analyzed all participants with questionnaires at either of those times (309) using a generalized linear mixed effects model which accounts for the correlation between measurements within a participant and assumes missing values are missing at random, we reached similar conclusions regarding the difference in parent-reported symptoms during a PE compared to baseline. We were also missing responses on the CFQ-R, although the baseline scores were available from more than 97% of the eligible participants.

In conclusion, pulmonary exacerbations in children with CF <6 years of age are common, generally manifested as cough, and are treated with oral antibiotics in the majority of cases. Nonetheless, they are associated with worse parent-reported outcomes. Thus, parent-reported outcomes could potentially serve as meaningful clinical endpoints in these young children. In addition, treatments that reduce the rate of exacerbations in very young patients may improve patient and family quality of life.

Acknowledgments

We would like to thank the patients and families who participated in the ISIS clinical trial. The ISIS study was jointly funded by the NIH (U01 HL 092931, UL 1RR025014) and CF Foundation Therapeutics Inc (ISIS07K1). The clinical coordinating center was the CF Foundation Therapeutics Network Coordinating Center and the data coordinating center was the Collaborative Health Studies Coordinating Center.

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Figure 1. Exacerbation rate (per person-year) by calendar month

Table 1

Participant characteristics at baseline, N=321.

Characteristic	N (%), or mean (standard deviation)
Age, yrs	2.3 (1.5)
Age Category	
<30 months	191 (60%)
30 months	130 (40%)
Gender	
Female	145 (45%)
Male	176 (55%)
Race/Ethnicity	
Non-Hispanic White	302 (94%)
Hispanic	13 (4%)
Other	6 (2%)
CF genotype ^a	311
F508del Homozygous	170 (53%)
F508del Heterozygous	114 (36%)
Other	37 (11%)
Weight percentile	
Height percentile	
Positive respiratory culture for <i>P. aeruginosa</i> ^b	129 (40%)
CFQ-R ^c	
Respiratory Symptoms Scale	87 (13)
Treatment Burden Scale	69 (20)
Physical Functioning Scale	95 (8)

^a Homozygous: F508del identified on both alleles; Heterozygous: F508del identified on 1 allele and mutation type for other allele either identified and not F508del, not identified, or not available

^b *Pseudomonas aeruginosa* isolated from respiratory culture at or any time prior to randomization.

^c N=313 for Respiratory Symptoms, 314 for Treatment Burden, and 108 for Physical Functioning

Table 2

Clinician-reported signs and symptoms of a pulmonary exacerbation (PE). Number of PEs (%) with reported sign or symptom by antibiotic type (not mutually exclusive) ^a.

Sign or Symptom	Type of antibiotic			
	Any ^b N=659	Oral N=636	Inhaled N=50	IV N=45
Increased cough	640 (97)	619 (97)	48 (96)	43 (96)
Increased chest congestion or change in sputum	202 (31)	191 (30)	19 (38)	23 (51)
New or increased adventitial sounds on lung exam	64 (10)	56 (9)	5 (10)	10 (22)
Worked harder than usual to breathe during physical activity	52 (8)	48 (8)	10 (20)	11 (24)
Increased work of breathing or respiratory rate	50 (8)	38 (6)	9 (18)	21 (47)
New lobar infiltrate or atelectasis on chest radiograph	15 (2)	13 (2)	2 (4)	5 (11)
Weight loss ≥ 5% of body weight or decrease across 1 major percentile in past 6 months	11 (2)	9 (1)	1 (2)	5 (11)
Oxygen saturation < 90% on room air or ≥ 5% decline from previous baseline	6 (1)	2 (0)	1 (2)	8 (18)
Hemoptysis	1 (0)	1 (0)	0 (0)	0 (0)
Number of symptoms reported ^c				
1	419 (64)	409 (64)	27 (54)	12 (27)
2	145 (22)	142 (22)	12 (24)	11 (24)
3 or more	95 (14)	85 (13)	11 (22)	22 (49)

^aExacerbations may have been treated with multiple antibiotic types. Symptoms in each column refer to those reported at the first use of that particular antibiotic type during an exacerbation.

^b“Any” refers to the first reported symptoms during an exacerbation, regardless of antibiotic type. For example, if an exacerbation was initially treated with oral and then with IV antibiotics, only the symptoms prompting oral antibiotic treatment would be recorded under “any.”

^cFor all 659 exacerbations, the number of “not available” responses for each of the 9 signs or symptoms, in same order as in table (“increased cough” to “hemoptysis”) were: 2, 87, 235, 101, 122, 328, 150, 265, and 100; 1 response was missing for all of the signs or symptoms except cough.

Table 3

Symptoms reported on weekly parent questionnaires from 222 participants with data at baseline^a and during week of onset of first exacerbation with completed questionnaire.

Symptom	N (%) with symptom, unless specified			P-value ^e
	Baseline ^a	During Exacerbation	Difference	
Coughing at times other than 10 minutes within saline treatment ^b	72 (33)	151 (68)	79 (35)	<0.0001
Cough up mucus ^b	35 (16)	95 (43)	60 (27)	<0.0001
Difficulty breathing	10 (5)	40(18)	30(13)	<0.0001
Working harder to breathe with physical activity	6 (3)	37 (17)	31 (14)	<0.0001
Feverish	5 (2)	26 (12)	21(10)	0.0001
More tired than usual	29(13)	60(27)	31 (14)	0.0004
Eating less than usual ^c	28 (13)	62 (28)	34 (15)	0.0001
Wheezing	10 (5)	27 (12)	17 (7)	0.001
Difficulty sleeping ^a	41 (19)	62 (28)	21 (9)	0.01
Cranky or fussy	76 (34)	78 (35)	2 (1)	0.8
At least 1 symptom above ^d	133 (61)	169 (78)	36 (17)	0.0001
Number of symptoms ^d				
Mean (Standard Deviation)	1.4 (1.6)	2.9 (2.5)	1.5 (2.8)	<0.0001
Median (Interquartile Range)	1 (0,2)	3 (1,5)	1 (0,3)	<0.0001

^aBaseline or the first time not during a PE

^bN=221 due to missing response.

^cN=220 due to missing responses

^dN=218 due to missing responses. Note that exacerbations were defined based on signs and symptoms reported by clinicians at the time of antibiotic prescription, whereas parents reported symptoms at home once per week. Thus, there were clinician-defined exacerbations in which no symptoms were reported by parents during the week of onset.

^eP-value from McNemar's test except for the number of symptoms where p-values are from paired t-test and Wilcoxon signed rank test.

Table 4

Concordance between clinician-reported symptoms of exacerbation and parent-reported symptoms from weekly parent questionnaire. N= 525 exacerbations from 225 participants with completed questionnaires during week of exacerbation onset.

Symptom	Concordance (%)
Clinician: Increased cough Parent: Coughing at times other than 10 minutes within saline treatment	70
Clinician: Increased chest congestion or change in sputum Parent: Coughing up mucus	55
Clinician: Worked harder than usual to breathe during physical activity ^a Parent: Working harder to breathe with physical activity ^a	81
Clinician: Increased work of breathing or respiratory rate Parent: Difficulty breathing	81

^aN=524 due to missing response

Table 5

Association between exacerbations and CFQ-R scale scores

CFQ-R Scale score	Baseline CFQ-R score as predictor and number of PEs as outcome ^a			PE rate as predictor and final CFQ-R score as outcome ^b		
	N	Rate Ratio (95% CI)	p-value	N	Coefficient (95% CI)	p-value
Respiratory Symptoms	313 ^c	1.08 (1.02, 1.14)	0.005	272	1.45 (0.58, 2.33)	0.001
Treatment Burden	314 ^c	1.01 (0.97, 1.05)	0.7	273	0.075 (-1.17, 1.32)	0.9
Physical Functioning	108 ^c	1.21 (1.07, 1.36)	0.003	92	1.21 (0.22, 2.19)	0.017

^a Poisson regression model with log of observation time as an offset term. Rate ratio is for a 10 point lower (worse) CFQ-R score.

^b Linear regression model with adjustment for baseline CFQ-R score. Coefficient is the number of points by which the final CFQ-R score is lower per 1 additional PE/year, on average, among persons with the same baseline CFQ-R score.

^c All 321 participants were eligible for the Respiratory Symptom and Treatment Burden scores, but only 109 (participants 3 years at baseline) were eligible for the Physical Functioning score.

Table 6

Association between exacerbations and other baseline characteristics. N=321

Participant Characteristic	Exacerbation Rate Ratio	
	Ratio ^a (95% CI)	p-value
Age, per standard deviation (SD)	1.04 (0.97, 1.13)	0.3
Gender, female : male	1.07 (0.92, 1.25)	0.4
Height percentile, per SD	1.03 (0.96, 1.11)	0.4
Weight percentile, per SD	1.03 (0.95, 1.11)	0.5
Genotype ^a		
F508del Homozygous: F508del Heterozygous	0.98 (0.83, 1.16)	0.9
Other : F508del Heterozygous	1.07 (0.83, 1.37)	0.6
Positive culture for <i>Pseudomonas aeruginosa</i>	0.88 (0.75, 1.03)	0.1

^aHomozygous: F508del identified on 2 alleles; Heterozygous: F508del identified on 1 allele and mutation type for other allele is either identified and not F508del, not identified, or not available