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Location and Duration of Treatment of Cystic Fibrosis Respiratory Exacerbations do not Affect Outcomes

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AT A GLANCE COMMENTARY: Scientific Knowledge on the Subject: Recurrent respiratory infections in individuals with cystic fibrosis may result in permanent loss of lung function, thus increasing morbidity and mortality. The optimal approach to treating these infections remains unclear. **What This Study Adds to the Field:** This study demonstrates no difference in short- and long-term lung function improvement, regardless of whether therapy is administered in inpatient or outpatient settings. Lung function measurements obtained during therapy suggest that longer courses of antibiotics (14-21 days) may not confer additional improvement in lung function over shorter courses (8-10 days).

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

Abstract

Rationale Individuals with cystic fibrosis (CF) are subject to recurrent respiratory infections (exacerbations) that often require intravenous antibiotic treatment and may result in permanent loss of lung function. The optimal means of delivering therapy remains unclear.

Objectives To determine whether duration and/or venue of intravenous antibiotic administration affect lung function.

Methods Data were retrospectively collected on 1535 subjects recruited by the US CF Twin and Sibling Study from US CF care centers between 2000-2007.

Main Results Long-term decline in FEV_1 following exacerbation was observed regardless of whether antibiotics were administered in the hospital (Mean: -3.3 percentage points, [95%CI: -3.9, -2.6], n=602 courses of therapy) or at home (-3.5, [-4.5, -2.5], n=232); this decline was not different by venue using *t*-tests (p=0.69) or regression (p=0.91). No difference in intervals between courses of antibiotics was observed between hospital (Median: 119 days, [IQR: 166], n=602) and home (98, [155], n=232) (p=0.29). Patients with greater drops in FEV_1 with exacerbations had worse long-term decline even if lung function initially recovered with treatment (p<0.001). Examination of FEV_1 measures obtained during treatment for exacerbations indicated that improvement in FEV_1 plateaus after 8-10 days of therapy.

Conclusions Intravenous antibiotic therapy for CF respiratory exacerbations administered in the hospital and in the home was found to be equivalent in terms of long-term FEV_1 change and interval between courses of antibiotics. Optimal duration of therapy (7-10 days) may be shorter

than current practice. Large prospective studies are needed to answer these essential questions for CF respiratory management.

Introduction

In 2008 the median predicted age of survival in the U.S. for people with cystic fibrosis (CF) was 37.4 years with the primary cause of morbidity and mortality being progressive obstructive lung disease.[1] Progression of lung disease may be hastened by recurrent severe respiratory infections termed respiratory exacerbations, which are characterized by a decline in spirometry, dyspnea, hypoxia, increased cough or sputum production, and/or weight loss. Traditional management includes aggressive airway clearance and antibiotics, the latter frequently administered intravenously. Despite effective symptomatic therapy, patients may not completely recover their baseline lung function. Thus, it is crucial to determine the most effective therapy for CF respiratory exacerbations. Unfortunately, due to the difficulty of performing randomized controlled trials, existing evidence is insufficient for many treatment issues.[2;3] Two of these key issues, namely the best site for delivery of intravenous antibiotic course (i.e. administration at home or in the hospital) and the optimal duration of therapy could be studied by examining outcomes in a large registry.

Outpatient intravenous therapy has gained widespread acceptance because of its advantages over hospitalization including: fewer absences from school or work and less disruption of family life,[4-7] decreased costs per treatment course,[4-8] and high patient satisfaction.[4-6] On the other hand, long-term costs may not be reduced in the outpatient setting due to the need for longer and more frequent courses of antibiotics,[9] and quality of life may not be better across all domains.[7;10] Additionally, several studies have documented no difference between inpatient and outpatient therapy in terms of compliance with antibiotic therapy,[5] or

improvement in forced expiratory volume in 1 second (FEV_1).[4-7;10-13] Conversely, other studies have shown a significantly greater improvement in FEV_1 after inpatient treatment compared to outpatient treatment.[9;14-17] It is important to recognize that most studies have consisted of fewer than 100 patients in a few clinical sites, which may result in limited power and clinic-specific biases. In addition, most studies have not followed patients for prolonged periods to determine if the choice of venue alters long-term lung function.

An equally pressing question is the optimal duration of therapy.[3] Although intravenous antibiotics are frequently prescribed for several weeks for CF respiratory exacerbations, treatment data from other lower respiratory tract infections, such as ventilator-associated pneumonia, suggests that shorter courses (8 days) may be as efficacious as longer courses (15 days).[18] This begs the question of whether shorter duration of therapy would provide the same clinical benefits as longer courses for the treatment of CF respiratory exacerbations, while reducing disruption of family life, costs, drug toxicity, allergic reactions, and/or bacterial resistance.

This study uses data from the U.S. Cystic Fibrosis Twin-Sibling Study for a large multi-center analysis of these questions. We hypothesize that inpatient therapy results in better outcomes (i.e., immediate improvement in lung function, arrest in long-term lung function decline, and longer intervals between courses of intravenous therapy) than outpatient therapy. We also seek to determine whether shorter duration of therapy leads to similar outcomes as longer duration, as measured by improvement in FEV_1.

Methods

Participants: 1535 individuals in 755 families were recruited through the U.S. Cystic Fibrosis Twin-Sibling Study under the oversight of the Johns Hopkins University IRB. All subjects met diagnostic criteria for CF.[19] All subjects used in the analyses attended CF Centers accredited by the U.S. Cystic Fibrosis Foundation. Informed written consent was obtained from all subjects and/or guardians. Pulmonary function and respiratory culture data collected by the Twin-Sibling Study were supplemented using the Cystic Fibrosis Foundation (CFF) Patient Registry. Therapy starting and ending dates and location of therapy were obtained from the CFF Patient Registry. Analysis was limited to courses of intravenous antibiotics ≤42 days in duration clinically designated for a "pulmonary exacerbation" in the CFF Patient Registry. The starting dates for treatment courses ranged from 1/1/2003 to 11/7/2007.

Lung Function: Raw forced expiratory volume in 1 second (FEV_1) measurements were converted to Knudson percentiles;[20] tests performed after lung transplantation and before age 6 years were excluded. Four averages of FEV_1 values reflected baseline lung function before and after a course of intravenous antibiotic therapy as well as lung function immediately before and after the course of antibiotics (Figure 1). Each of these measures was calculated for each exacerbation and contains data from only the time periods outlined in Figure 1. The mean (±SD) number of pulmonary function tests averaged for each lung function measure were 7.1 ± 5.0, 1.3 ± 0.6, 1.3 ± 0.6, and 6.7 ± 5.1 for Baseline FEV_1, Pre-therapy FEV_1, Post-therapy FEV_1, and New Baseline FEV_1, respectively. Three indices were derived to describe changes in lung function. The primary outcome, Baseline Change, was intended to provide a measure of long-term change following a course of therapy, thus an indicator of long-term prognosis. Immediate Recovery was intended to provide a measure of short-term recovery of FEV_1 with treatment.

Sick Decline was intended to provide a measure of the magnitude of a respiratory exacerbation with the decline in FEV_1. Owing to the nature of frequent exacerbations in many subjects with CF, periods of lung function overlapped for some exacerbations. However, the mean number of years of pulmonary function test data available prior to the start date of an exacerbation was 9.9 ± 5.7 years; only 3% of the 1278 exacerbations used in the study had less than 1 year of baseline pulmonary function test data. For the duration of therapy analysis, normalized improvement in FEV_1 was calculated by subtracting Pre-therapy FEV_1 from the FEV_1 measurement obtained during therapy, dividing by the Baseline FEV_1 and then multiplying by the mean baseline FEV_1 for the population mean for this analysis (68.8%).

Of the 1535 individuals in the Twin-Sibling Study, only 1327 had pulmonary test data available; these subjects were older (17.3 ± 9.2 yrs) than the 208 subjects without pulmonary function test (PFT) data (10.3 ± 20.3) (p<0.0001) as younger patients may not have had exacerbations or accumulated enough lung function data to establish baselines (Supplemental Table 1). The dataset for studying the effect of venue included 1278 courses of therapy in 479 individuals with all four measures of lung function in Table 1 for analysis. The 848 individuals with PFT data who were not used in the venue analyses were younger (16.1 ± 9.5 yrs) and more likely to be male (54.8%) than the 479 individuals whose PFT data was used (19.4 ± 8.3 yrs, p<0.0001; 47.4% male, p=0.009).

A second set of FEV_1 measurements obtained during intravenous therapy (up to and including the final day of therapy) was used for studying duration of therapy. Exacerbations without Baseline FEV_1 or Pre-therapy FEV_1 were excluded. The analysis was limited to the first

22 days of therapy as the number of FEV_1 measurements available for any particular day was fewer than 40 after day 22 of therapy. This second dataset included 2426 FEV_1 measurements obtained during 1331 exacerbations in 492 subjects (Supplemental Figure 2). The 835 individuals with PFT data who were not used in the duration analyses were younger (16.1 ± 9.4 yrs) than the 492 individuals whose PFT data was used (19.2 ± 8.4 yrs, $p<0.0001$).

Other variables: "Hospital" and "Home" were defined as courses of intravenous antibiotics administered entirely in the hospital or the outpatient setting, respectively. Courses of therapy which included time spent both in the hospital and home venue were defined as "Combination" and analyzed separately. Status for *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Burkholderia cepacia* (*B. cepacia*) complex for each exacerbation were based on whether the subject had a positive respiratory culture in any data collected by the Twin-Sibling Study or the CFF for *P. aeruginosa* or *B. cepacia* complex, respectively, before or by the start date of therapy. For cystic fibrosis transmembrane conductance regulator (*CFTR*) genotype, subjects were classified by number of F508del mutations they carried. Time until next exacerbation was calculated as the time in days between the last date of intravenous antibiotic therapy for an exacerbation and the first date of intravenous antibiotic therapy for the next exacerbation.

Data Analysis: Statistical methods used include Student's *t* tests, ANOVA tests, chi-square tests, and stepwise regression analysis (Generalized Estimating Equations (GEE): clustered by individual). Regression analysis clustered by family was also performed, but the significant results did not change. For stepwise regression, predictor variables with *p* values <0.05 were dropped, excepting the variables of age, gender, and total days of therapy in any

regression comparing home therapy vs. hospital therapy as these factors significantly differed between these two groups. Intercooled Stata 10 (StataCorp LP., College Station, TX) was used for all statistical analyses.

Results

Demographics: Courses of antibiotic therapy within the dataset were divided into three groups, Home, Hospital, and Combination as described above. Individual subjects may have received treatment in different venues on separate occasions. Groups differed significantly by gender, age, and duration of therapy (Table 1). Subjects receiving therapy entirely in the home setting were more likely to be female than in other groups. This gender phenomenon has been reported previously.[13;14] When looking at the data by exacerbation, subjects who received therapy entirely in the hospital were younger than other groups and those receiving therapy entirely in the home were older than other groups. Those receiving therapy entirely in the hospital were treated for fewer days compared to other groups. Average lung function before and after therapy were not different between the groups treated entirely in the hospital or the home.

Therapy for an exacerbation does not necessarily preserve long-term lung function: Patients in all 3 groups experienced a decrease in FEV_1 just prior to treatment for an exacerbation, generally followed by recovery to the previous baseline immediately after treatment (Figure 2). More importantly, the new baseline FEV_1 following an exacerbation was lower than the previous baseline prior to the exacerbation, regardless of venue ($p<0.0001$).

Hospital Therapy does not produce better outcomes than Home therapy: Using both t-tests and adjusted linear regression, no differences were found in long-term lung function

between inpatient vs. outpatient therapy. Using the courses of therapy from Table 1, there was no difference in Baseline Change following therapy or time until next respiratory exacerbation requiring intravenous antibiotics between home and hospital therapy courses (Table 2). Subjects in the Hospital group had a greater improvement of lung function immediately after therapy (Immediate Recovery: 9.2 predicted percentage points, [95%CI: 8.2, 10.2]) vs. those in the Home group (5.0, [3.8, 6.1]); however, the Hospital group had a greater initial decrease in lung function with an exacerbation (Sick Decline: -8.6, [-9.5, -7.7]) vs. the Home group (-5.6, [-6.6, -4.6]). Analyses also were performed with these changes as a percentage of Baseline FEV_1, but the results were not altered. Findings were similar if all courses of therapy with any time spent in the hospital (Hospital only group and the Combination group) (Baseline Change: -3.4 ± 8.8 [95%CI: -3.9, -2.9], n=1046) were compared to all courses treated entirely in the home setting (-3.5, [-4.5, -2.5], n=232) (p=0.83).

Bias may arise in the previous analysis given that an individual subject may not be represented in both groups. Thus, courses of therapy from 32 subjects who had data from separate treatment courses in both entirely in the hospital and entirely in the home are compared in Table 2; the most recent hospital and home courses of therapy for each subject were used for this analysis. Courses of therapy were temporally separated by a mean (±SD) of 1.29 ± 1.00 years [Range: 0.1 – 3.98 years] with the outpatient therapy course preceding the inpatient one in 18 subjects. Paired *t* tests demonstrated no differences in Baseline Change or time until next antibiotic course.

Since the Hospital and Home therapy groups differed statistically by age, gender distribution, and total days of therapy (Table 1), linear regression modeling was employed to

adjust for these factors as well as for other potential predictors, including *P. aeruginosa* and *B. cepacia* complex statuses, *CFTR* genotype, baseline lung function (Baseline FEV_1), degree of illness (Sick Decline), and the predictor of interest, therapy venue (Hospital or Home). Examining the long-term outcome (Baseline Change), the variable for venue drops out of the final regression model (Supplemental Table 3), but the final model predicts that subjects with a greater decline in lung function prior to initiation of therapy experience a worse long-term decline following that course of therapy (Sick Change $p<0.001$). This holds true even if the final model is adjusted for Immediate Recovery (Supplemental Table 4: Sick Decline $p<0.001$). This implies that patients with drastic drops in lung function should be monitored more closely following treatment, for even with recovery of lung function, they remain at higher risk for greater long-term decline.

Performing a separate regression analysis on short-term outcome (Immediate Recovery), the variable for venue also failed to reach significance in the final regression model (Supplemental Table 5), suggesting that location may be less important in both short-term and long-term outcomes than the other factors included in the models. Finally, subjects with a greater initial decline in lung function also have a greater improvement in FEV_1; the coefficient of the final model suggests that on average subjects regain 72% of their lost lung function immediately after completing antibiotic therapy. Of note, shorter courses of antibiotics were associated both better short and long-term outcomes.

The venue of Combination courses of antibiotics does not affect long-term lung function: Many courses of intravenous antibiotics are initiated in an inpatient setting and completed at home. A secondary question of interest was whether the duration of the inpatient

admission alters outcomes. For this analysis, regression modeling identical to the previous analyses was used, excepting that the location variable represents the percentage of time during a course of intravenous antibiotics that was spent in the hospital (Mean ± SD: 32.5 ± 18.4%). Examining the long-term outcome of Baseline Change, the percentage of time spent in the hospital as a variable was not significant (Supplemental Table 6). The significant predictors in the final model for worse long-term lung function decline included greater initial drops in lung function with illness, the presence of *P. aeruginosa*, and longer duration of therapy. However, a greater percentage of time spent in the hospital for treatment of an exacerbation was associated with a shorter interval until next exacerbation requiring intravenous antibiotics, even after correcting for baseline lung function and total length of therapy using regression (p<0.001). This may represent the presence of other medical complications, such as diabetes, that may lead to a subsequent exacerbation more rapidly.

Longer Duration of Therapy does not provide better outcomes: In our regression analyses of venue, we observed that shorter courses of intravenous antibiotics were associated with better FEV_1 outcomes. By stratifying by duration of therapy (Figure 3), it is observed that subjects receiving shorter courses of antibiotics tend to have better baseline lung function and improvement in FEV_1 with therapy. Thus, in examining improvement in FEV_1 during an exacerbation, baseline lung function must be taken into account. In Figure 4, the mean improvement in FEV_1 (±SE) from Pre-therapy FEV_1 to a given day of intravenous therapy is depicted; this mean improvement has been corrected for Baseline FEV_1 as well as normalized based on the population mean Baseline FEV_1 (68.8%) to provide more meaningful estimates of

improvement. In Figure 4, FEV_1 continues to improve through day 8 of therapy and reaches maximal improvement on day 10. Shorter courses were not associated with a shorter interval between courses of intravenous antibiotics. Using 2417 exacerbations in 524 subjects where baseline FEV_1 and time until next exacerbation were known, duration of therapy did not predict time until next exacerbation (p=0.11) using linear regression with adjustment for baseline FEV_1.

Discussion

Treatment of respiratory exacerbations in CF patients with intravenous antibiotics remains a cornerstone in arresting or mitigating long-term decline in lung function. Our data suggests that although intravenous antibiotic therapy leads to an immediate improvement lung function in the majority of patients, these patients have a lower baseline FEV_1 in the subsequent year. This finding is consistent, regardless of the venue or duration of therapy, and highlights the need for clinicians to employ therapies that reduce the likelihood of exacerbations. Furthermore, clinicians should not be necessarily reassured with complete recovery of lung function in patients who had a greater drop with illness. These patients remain at a higher risk for long-term decline. These results demonstrate that determining an optimal approach to the treatment of pulmonary exacerbations is of vital importance to the CF community.

Currently, there is little evidence to direct physicians' therapies of exacerbations. Prior studies have provided conflicting results as to the efficacy of intravenous antibiotic therapy administered at home compared to that administered in the hospital.[4-17] The only prospective randomized study of the venue of antibiotic administration for respiratory exacerbations in CF

patients published to date found that there was no difference in lung function by therapy venue.[7] Our multi-center study also did not observe any differences in short-term improvement in FEV_1 (Immediate Recovery) when therapy was performed at home compared to in the hospital setting.

We also did not observe any differences in long-term lung function decline (Baseline Change) either by examining the entire study population, separate home and hospital courses within the same individual, or adjusted linear regression, which includes correction for age and duration of therapy. In subjects whose antibiotic therapy was divided between the hospital and home settings, the percentage of therapy administered in a hospital setting did not alter long-term lung function decline either. There have been two prior studies examining long-term (1 year) changes in lung function. Both found that the decline in FEV_1 was significantly worse in the group treated at home.[14;17] In Thornton *et al.* the patients were older (Mean: 26 years; Range: 16 – 47) and in Termoz *et al.* the patients were younger (Mean 13.4 years; Range: 4 – 33) and hospital and home courses of therapy were more similar in duration than in our study. A key design difference between our study and the prior studies is that in both of these studies subjects categorized as "Home" may have received up to 40% of their therapy in the hospital, and vice versa for those categorized as "Hospital." Also, both of these studies were conducted in Europe where practice patterns in the home and hospital may vary from the U.S. leading to the differing observed results.

The optimal duration of therapy for a pulmonary exacerbation is also unknown. By examining FEV_1 measurements obtained during courses of antibiotic therapy, we observed that the majority of improvement in lung function may occur within the first week of therapy with a

plateau of improvement within 8 to 10 days of initiation of therapy. This suggests that courses of 14 to 21 days duration may not provide additional benefit for many patients. Furthermore, the interval between courses of intravenous antibiotics was not affected by duration of therapy. These results imply that shortening duration of therapy may yield similar results while potentially lessening disruption of family life, healthcare costs and the risk of drug toxicity. In contrast, Redding *et al.* noted continuous improvement in FEV_1 over 14 days of therapy.[21] However, this study was limited to 17 subjects with more severe lung disease than our population (Mean admission FEV_1: 26 ± 9 %). Prospective trials to assess improvement in FEV_1 and other clinical parameters to determine optimal duration of intravenous antibiotics as well as risk factors for slower improvement that may require longer courses of antibiotics are needed.

Limitations to this study include the absence of an objective pre-determined definition for a respiratory exacerbation. This study is subject to the treating clinician's judgment for what constitutes a "pulmonary exacerbation" requiring intravenous antibiotics, but this range of clinical criteria may better reflect current practices. Additionally, the length of therapy is also based on the clinician's judgment and is likely influenced by factors other than FEV_1, such as dyspnea, fever, and/or continued cough, which were not assessed in this study. We also were unable to assess other factors in the decision as where to treat, including, but not limited to, social support, compliance, payer restrictions, other co-morbidities, and/or families' prior experience. Also, the analyses' requirements of complete pulmonary function data prior to and after therapy may exclude subjects who are: non-compliant with recommended follow-up, in better health and not requiring frequent pulmonary function testing, and under the age of 6

years old who cannot reliably perform pulmonary function testing. Additionally, no difference between home and hospital therapy may have been observed due to possible biases inherent in using averages of lung function, rather than the highest lung function in a given time period, which may bias against hospital-treated patients with frequent exacerbations who have brief episodes of decreased lung function, and in using data from a family-based study as the experience for siblings with CF may be different than that of a single child with CF. Subjects who participate in the Twin-Sibling Study may be more motivated than the general CF population, and thus may have increased compliance with antibiotics and chest physiotherapy when treated at home. These subjects are also members of families where more than one sibling has CF, thus these families may be more adept with home care. Also, our study was biased towards older subjects who had more data available for analyses, and thus our findings may not be as robust for younger children. Finally, although a number of key demographic factors were modeled, there may be unmeasured differences between Hospital and Home groups (e.g. differential use of oral antibiotics prior to intravenous antibiotics) that could result in the possible non-significance of our findings.

In summary, respiratory exacerbations in individuals with CF hasten progression of chronic lung disease and decline of lung function. Successful treatment of exacerbations is essential in preserving lung function, and key therapeutic decisions include venue and duration of antibiotic administration. Using a large multicenter population with longitudinal data, our findings demonstrate that venue of intravenous antibiotic therapy for clinician-defined respiratory exacerbations does not affect long-term decline in FEV_1 and that the majority of improvement in lung function may occur within the first 8 to 10 days of therapy. Given the

decline in baseline FEV1 after an exacerbation, preventing exacerbations may ultimately be more important than the approach taken to treat the exacerbation.

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Figure Legends

Figure 1. Lung Function Measures

Figure 2. Mean Lung Function over Time (Based on Table 1 data): This figure provides the mean values for each measure of lung function before and after a respiratory exacerbation by venue of treatment. As can be seen, all groups experience a substantial decline in lung function with an exacerbation, followed by recovery in some cases back to the original baseline, but long-term lung function is decreased compared to the original baseline lung function. 95% confidence intervals for all lung function measures can be found in Supplemental Table 2.

Figure 3. Change in FEV_1 by Duration of Therapy: This figure provides the mean values for each measure of lung function before and after a respiratory exacerbation by duration of treatment for the same population depicted in Figure 2. Subjects who receive longer courses of intravenous antibiotics tend to have worse lung function and do not recover all lost lung function immediately following a treatment course. In all groups long-term lung function is decreased compared to the original baseline lung function. 95% confidence intervals for all lung function measures can be found in Supplemental Table 2.

Figure 4. Mean Improvement in FEV_1 by Day of Therapy: This figure demonstrates the mean (±SE) improvement in lung function corrected and normalized (mean baseline FEV_1: 68.8%) for baseline lung function by day of intravenous therapy using pulmonary function tests obtained during therapy. The numbers above each reflect the number of pulmonary function tests contributing to each datapoint. As can be seen, lung function demonstrates improvement until approximately 8-10 days of therapy, where it then plateaus. The analysis was limited to the first 22 days of therapy as the number of FEV_1 measurements available for any particular day was fewer than 40 after day 22 of therapy.

Table 1. Demographics

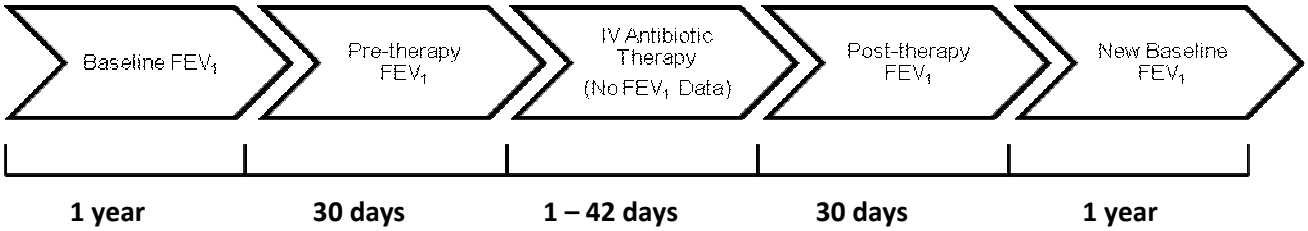
		All	Hospital Only	Home Only	Combination: Hospital and Home	*p* value (Hosp vs. Home)*
Data by Subject	**Number of subjects**	479	261	114	248	-
	Mean courses of antibiotics per subject in dataset	2.7 ± 2.4	-	-	-	-
	Age at most recent FEV_1 (yrs) (Mean ± SD)	19.4 ± 8.3	18.2 ± 6.5	22.3 ± 9.4	20.4 ± 9.0	**<0.0001**
	Gender (% Male)	47.4	49.0	34.2	44.0	**0.01**
	CFTR (% F508del homozygotes)	49.2 (n = 478)	51.2 (n = 260)	43.0	48.6 (n = 247)	0.35
Data by Therapy Course	**Number of courses**	1278	602	232	444	-
	Age at start of therapy (yrs) (Mean ± SD)	17.8 ± 8.0	16.2 ± 6.1	22.0 ± 10.0	17.8 ± 8.2	**<0.0001**
	***P. aeruginosa* (% positive)**	96.4	95.7	97.8	96.6	0.14
	***B. cepacia* (% positive)**	10.6	11.5	9.9	9.9	0.52
	Days treated in hospital (Mean ± SD)	-	12.7 ± 5.3	-	6.0 ± 4.3	-
	Days treated at home (Mean ± SD)	-	-	18.9 ± 7.4	12.5 ± 5.7	-
	Total days of treatment (Mean ± SD)	15.8 ± 6.7	12.7 ± 5.3	18.9 ± 7.4	18.5 ± 6.0	**<0.0001**
	Baseline FEV_1 (Mean ± SD)	68.4 ± 22.0	67.4 ± 22.4	65.1 ± 22.1	71.4 ± 21.2	0.17
	Pre-therapy FEV_1 (Mean ± SD)	60.4 ± 22.0	58.8 ± 22.0	59.5 ± 22.3	63.0 ± 21.5	0.68
	Post-therapy FEV_1 (Mean ± SD)	68.7 ± 23.4	67.9 ± 23.3	64.4 ± 23.5	72.0 ± 23.0	0.05
	New baseline FEV_1 (Mean ± SD)	64.9 ± 23.3	64.1 ± 23.1	61.5 ± 23.5	67.8 ± 23.3	0.15

*These *p* values reflect the difference between the hospital and home categories. *P* values were determined using student's t and chi-square tests.

Table 2. Change in FEV_1: Hospital vs. Home

Mean ± SD [95%CI]		**Hospital Only (n = 602 courses of therapy)**	**Home Only (n = 232 courses of therapy)**	***p* value**
All courses from Table 1 (n = 602 hospital only courses & 232 home only courses)	**Sick Decline** = ($PreFEV_1$ – Baseline FEV_1)	-8.6 ± 11.2 [-9.5, -7.7]	-5.6 ± 7.8 [-6.6, -4.6]	**0.0001**
	Immediate Recovery = ($PostFEV_1$ – $PreFEV_1$)	9.2 ± 12.4 [8.2, 10.2]	5.0 ± 9.3 [3.8, 6.1]	**<0.0001**
	Baseline Change = (New Baseline – Baseline)	-3.3 ± 8.4 [-3.9, -2.6]	-3.5 ± 7.6 [-4.5, -2.5]	0.69
	Days until next exacerbation: Median (IQR)	119 (55,221) (n = 517)	98 (49, 204) (n = 198)	0.29
Separate hospital and home courses of therapy in the same individual (n = 32 subjects)	**Sick Decline**	-7.3 ± 12.7 [-11.9, -2.7]	-7.5 ± 8.3 [-10.4, -4.5]	0.94
	Immediate Recovery	7.3 ± 14.0 [2.3, 12.3]	5.4 ± 10.0 [1.8, 9.0]	0.49
	Baseline Change	-4.4 ± 8.2 [-7.4, -1.5]	-3.8 ± 6.9 [-6.3, -1.3]	0.72
	Days until next exacerbation: Median (IQR)	80 (37, 204) (n = 25)	54 (44, 138) (n = 25)	0.89

Figure 1. Lung Function Measures



Variable	Description
Baseline FEV_1	Average of all FEV_1 values in the 1 year prior to 30 days before the start date of therapy
Pre-therapy FEV_1	Average of all FEV_1 values in the 30 days prior to the start date of therapy
Post-therapy FEV_1	Average of all FEV_1 values in the 30 days following the end date of therapy
New Baseline FEV_1	Average of all FEV_1 values in the 1 year following 30 days after the end date of therapy
Baseline Change	New Baseline FEV_1 – Baseline FEV_1
Immediate Recovery	Post-therapy FEV_1 – Pre-therapy FEV_1
Sick Decline	Pre-therapy FEV_1 – Baseline FEV_1

Figure 2. Mean Lung Function over Time (Based on Table 1 data)

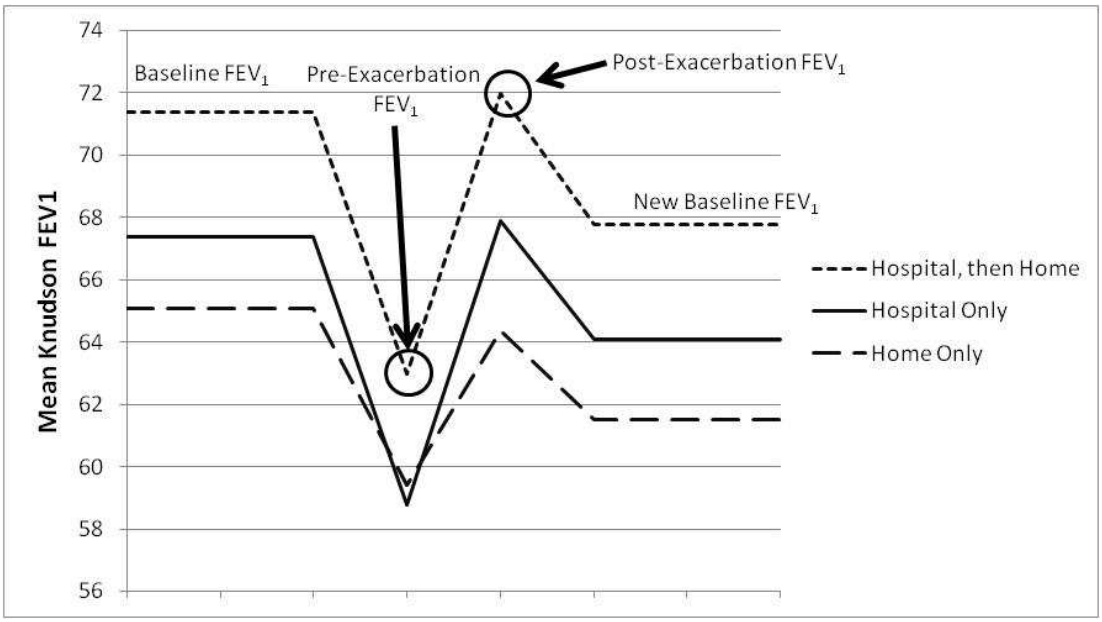


Figure 3. Change in FEV_1 by Duration of Therapy

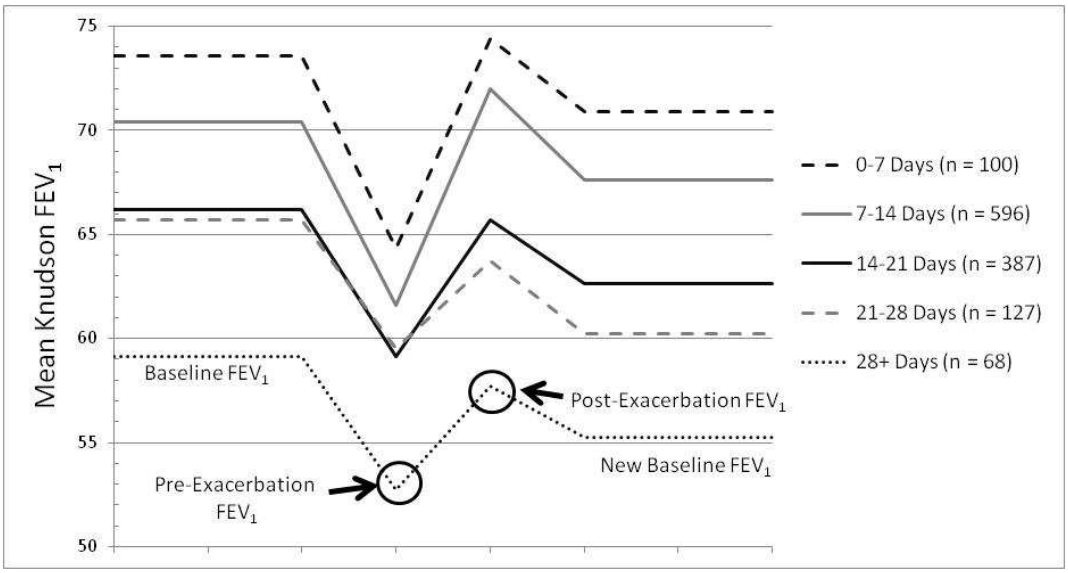
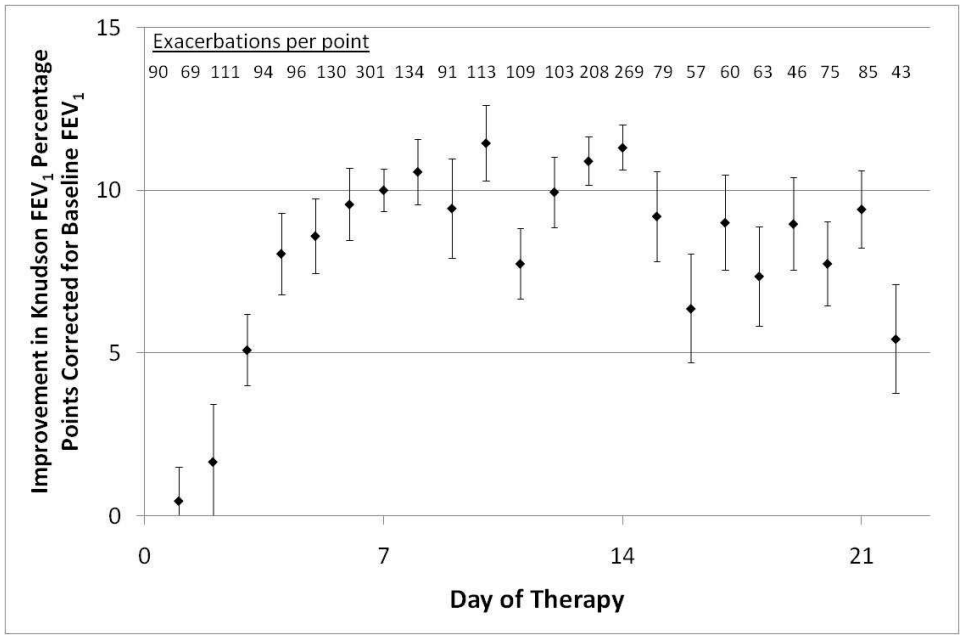


Figure 4. Mean Improvement in FEV_1 by Day of Therapy



Location and Duration of Treatment of Cystic Fibrosis Respiratory Exacerbations do not Affect Outcomes

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Garry R. Cutting, M.D., Kathleen M. Naughton, C.R.N.P.,
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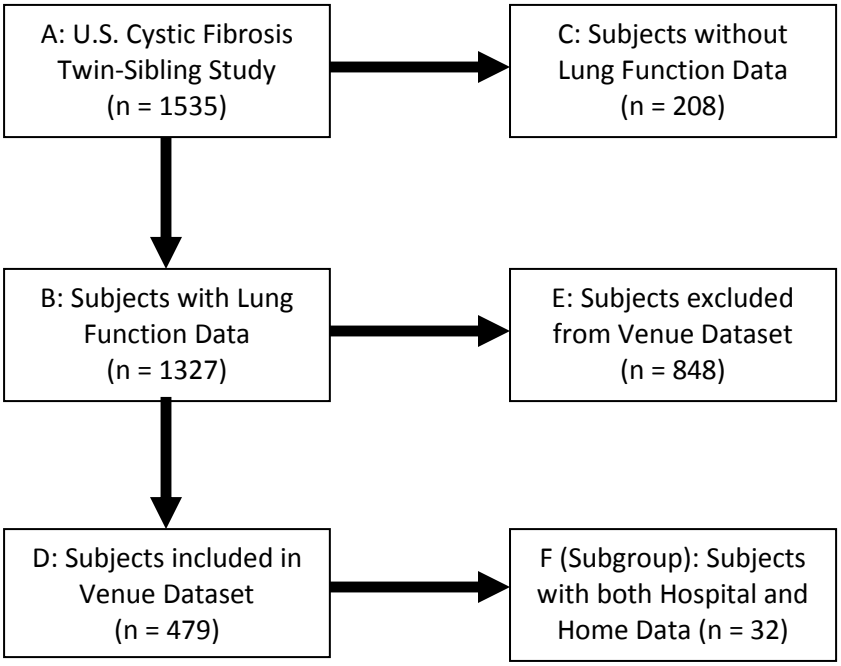
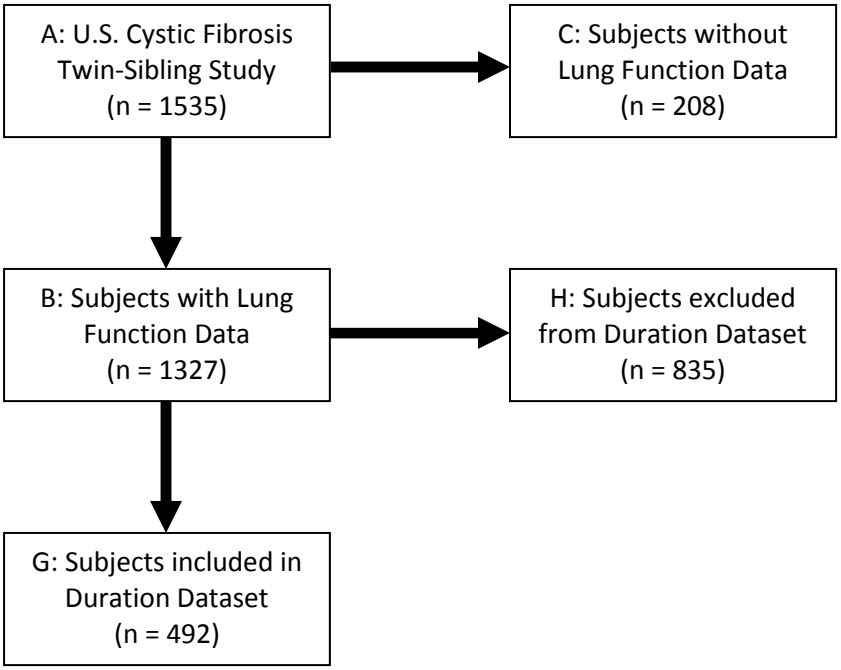
ONLINE DATA SUPPLEMENT

Supplemental Figure 1. Derivation of Study Population for Venue



Supplemental Figure 2. Derivation of Study Population for Duration



Supplemental Table 1. Demographics of Study Populations

	A Twin-Sibling Study	B Any lung function data[1]	C No lung function data[1]	D Venue of Therapy Group[2]	E Excluded from Venue[2]	F Subgroup for Hospital vs. Home	G Duration of Therapy Group[3]	H Excluded from Duration[3]
n	1535	1327	208	479	848	32	492	835
Age (yrs)[4]	16.3 ± 11.6	17.3 ± 9.2	10.3 ± 20.3	19.4 ± 8.3	16.1 ± 9.5	22.1 ± 7.22	19.2 ± 8.4	16.1 ± 9.4
Gender (% Male)	51.8 (n=1534)	52.2	49.8 (n=207)	47.4	54.8	75.0	49.2	53.9
***CFTR* (% DF508 homozygotes)**	49.3 (n=1524)	49.2 (n=1323)	49.8 (n=201)	49.2 (n=478)	49.2 (n=845)	40.6	50.1 (n=491)	48.7 (n=832)

[1] Comparing groups B and C: Age *t* test *p* value<0.0001, gender chi square=0.52, *CFTR* chi square=0.89.
[2] Comparing groups D and E: Age *t* test *p* value<0.0001, gender chi square=0.009, *CFTR* chi square=0.98.
[3] Comparing groups G and H: Age *t* test *p* value<0.0001, gender chi square=0.10, *CFTR* chi square=0.62.
[4] Age is calculated from the last pulmonary function test used in the study or from 12/31/2007 for subjects without pulmonary function test data.

Supplemental Table 2. Means and Confidence Intervals for Lung Function Measures by Group for Figures 2 and 3

Category	Group	n	Baseline FEV_1	Pre-therapy FEV_1	Post-therapy FEV_1	New Baseline FEV_1
Venue (Figure 2)	**Hospital Only**	602	67.4 [65.6, 69.2]	58.8 [57.0, 60.5]	67.9 [66.1, 69.8]	64.1 [62.3, 66.0]
	Home Only	232	65.1 [62.2, 67.9]	59.5 [56.6, 62.4]	64.4 [61.4, 67.5]	61.5 [58.5, 64.6]
	Combination: Hospital & Home	444	71.4 [69.4, 73.3]	63.0 [61.0, 65.0]	72.0 [69.8, 74.1]	67.8 [65.6, 70.0]
Duration (Figure 3)	**≤7 days**	100	73.6 [68.4, 78.8]	64.3 [59.4, 69.2]	74.4 [69.3, 79.5]	70.9 [65.7, 76.2]
	8-14 days	596	70.4 [69.7, 72.2]	61.6 [59.9, 63.3]	72.0 [70.2, 73.9]	67.6 [65.7, 69.4]
	15-21 days	387	66.3 [64.1, 68.5]	59.1 [56.8, 61.3]	65.7 [63.4, 68.0]	62.6 [60.3, 64.9]
	22-28 days	127	65.7 [62.3, 69.2]	59.5 [55.8, 63.2]	63.7 [59.9, 67.4]	60.2 [56.5, 63.9]
	>28 days	68	59.2 [54.2, 64.1]	52.7 [48.1, 57.4]	57.7 [52.7, 62.8]	55.2 [50.1, 60.2]

Supplemental Table 3. Predictive Models for Baseline Change (n = 832 therapy courses, 342 subjects)

Regression Coefficient (coefficient *p* value)	**Univariate Models**	**Multivariate Model***	**Final Model†**
Gender (Female = 1, Male = 0)	0.06 (0.93)	0.10 (0.89)	0.05 (0.94)
Number of CFTR F508del alleles (0 - 2)	-0.33 (0.57)	-0.23 (0.67)	
Age at start of therapy (Years)	-0.01 (0.78)	-0.06 (0.23)	-0.05 (0.28)
***P. aeruginosa* present** (Yes = 1; No = 0)	-1.32 (0.42)	-1.70 (0.39)	
***B. cepacia* complex present** (Yes = 1; No = 0)	-0.58 (0.64)	-0.04 (0.97)	
Duration of therapy (Days)	**-0.11 (0.02)**	**-0.15 (0.004)**	**-0.15 (0.001)**
Baseline FEV_1 (Knudson percentage)	-0.03 (0.05)	-0.01 (0.50)	
FEV_1 drop prior to therapy (Sick Decline) (Baseline FEV_1 – PreFEV_1)	**0.26 (<0.001)**	**0.27 (<0.001)**	**0.27 (<0.001)**
Location (Home = 1, Hospital = 0)	-0.30 (0.69)	0.08 (0.91)	

*Multivariate Model overall *p* value: <0.0001

†Final Model overall *p* value: <0.0001; r = 0.36; residual kurtosis: 5.64.

Supplemental Table 4. Predictive Models for Baseline Change (n = 832 therapy courses, 342 subjects)

Regression Coefficient (coefficient *p* value)	**Univariate Models**	**Multivariate Model***	**Final Model†**
Gender (Female = 1, Male = 0)	0.06 (0.93)	0.03 (0.96)	0.07 (0.91)
Number of CFTR F508del alleles (0 - 2)	-0.33 (0.57)	-0.11 (0.81)	
Age at start of therapy (Years)	-0.01 (0.78)	-0.04 (0.32)	-0.04 (0.35)
***P. aeruginosa* present** (Yes = 1; No = 0)	-1.32 (0.42)	-1.39 (0.37)	
***B. cepacia* complex present** (Yes = 1; No = 0)	-0.58 (0.64)	-0.61 (0.58)	
Duration of therapy (Days)	**-0.11 (0.02)**	-0.08 (0.08)	-0.07 (0.07)
Baseline FEV_1 (Knudson percentage)	-0.03 (0.05)	-0.002 (0.91)	
FEV_1 drop prior to therapy (Sick Decline) (Baseline FEV_1 – PreFEV_1)	**0.26 (<0.001)**	**0.54 (<0.001)**	**0.54 (<0.001)**
FEV_1 recovery with therapy (Immediate Recovery) (PostFEV_1 – PreFEV_1)	**0.08 (0.02)**	**0.38 (<0.001)**	**0.37 (<0.001)**
Location (Home = 1, Hospital = 0)	-0.30 (0.69)	0.32 (0.66)	

*Multivariate Model overall *p* value: <0.0001

[†]Final Model overall *p* value: <0.0001; r = 0.54; residual kurtosis: 5.19.

Supplemental Table 5. Predictive Models for Immediate Recovery (n = 832 therapy courses, 342 subjects)

Regression Coefficient (coefficient *p* value)	Univariate Models	Multivariate Model[*]	Final Model[†]
Gender (Female = 1, Male = 0)	-0.27 (0.79)	0.17 (0.81)	-0.04 (0.95)
Number of CFTR F508del alleles (0 - 2)	-0.09 (0.91)	-0.32 (0.59)	
Age at start of therapy (Years)	**-0.23 (<0.001)**	-0.04 (0.30)	-0.03 (0.43)
***P. aeruginosa* present** (Yes = 1; No = 0)	-1.82 (0.59)	-0.80 (0.64)	
***B. cepacia* complex present** (Yes = 1; No = 0)	1.85 (0.35)	1.52 (0.20)	
Duration of therapy (Days)	**-0.33 (<0.001)**	**-0.20 (<0.001)**	**-0.21 (<0.001)**
Baseline FEV_1 (Knudson percentage)	**0.08 (<0.001)**	-0.02 (0.15)	
FEV_1 drop prior to therapy (Sick Decline) (Baseline FEV_1 – PreFEV_1)	**-0.73 (<0.001)**	**-0.72 (<0.001)**	**-0.72 (<0.001)**
Location (Home = 1, Hospital = 0)	**-4.23 (<0.001)**	-0.63 (0.46)	

[*]Multivariate Model overall *p* value: <0.0001

[†]Final Model overall *p* value: <0.0001; r = 0.66; residual kurtosis: 4.96.

Supplemental Table 6. Predictive Models for Baseline Change (n = 442 combination therapy courses, 247 subjects)

Regression Coefficient (coefficient *p* value)	Univariate Models	Multivariate Model[*]	Final Model[†]
Gender (Female = 1, Male = 0)	-1.06 (0.34)	-0.79 (0.45)	
Number of CFTR F508del alleles (0 - 2)	0.03 (0.97)	-0.08 (0.92)	
Age at start of therapy (Years)	-0.02 (0.76)	0.01 (0.93)	
***P. aeruginosa* present** (Yes = 1; No = 0)	-3.41 (0.08)	**-4.11 (0.03)**	**-4.42 (0.03)**
***B. cepacia* complex present** (Yes = 1; No = 0)	-2.26 (0.19)	-1.77 (0.27)	
Duration of therapy (Days)	**-0.15 (0.03)**	**-0.155 (0.03)**	**-0.18 (0.01)**
Baseline FEV_1 (Knudson percentage)	0.01 (0.82)	0.01 (0.59)	
FEV_1 drop prior to therapy (Sick Decline) (Baseline FEV_1 – PreFEV_1)	**0.28 (<0.001)**	**0.29 (<0.001)**	**0.29 (<0.001)**
Percentage of time spent in the hospital (Days in Hospital/Total Days of Treatment)	-1.63 (0.46)	-0.71 (0.75)	

[*]Multivariate Model overall *p* value: <0.0001

[†]Final Model overall *p* value: <0.0001; r = 0.34; residual kurtosis: 4.18.