Location and Duration of Treatment of Cystic Fibrosis Respiratory Exacerbations Do Not Affect Outcomes

J. Michael Collaco[1], Deanna M. Green[1], Garry R. Cutting[2], Kathleen M. Naughton[2], and Peter J. Mogayzel, Jr[1]

[1]Eudowood Division of Pediatric Respiratory Sciences and [2]McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, Maryland

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 or venue of intravenous antibiotic administration affect lung function.**
Methods: **Data were retrospectively collected on 1,535 subjects recruited by the US CF Twin and Sibling Study from US CF care centers between 2000 and 2007.**
Measurements and Main Results: **Long-term decline in FEV_1 after exacerbation was observed regardless of whether antibiotics were administered in the hospital (mean, −3.3 percentage points [95% confidence interval, −3.9 to −2.6]; n = 602 courses of therapy) or at home (mean, −3.5 percentage points [95% confidence interval, −4.5 to −2.5]; n = 232 courses of therapy); 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 d [interquartile range, 166]; n = 602) and home (median, 98 d [interquartile range, 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 7–10 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 d) may be shorter than current practice. Large prospective studies are needed to answer these essential questions for CF respiratory management.**

Keywords: cystic fibrosis; FEV_1; exacerbation; antibiotic; outcome

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.

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 d) may not confer additional improvement in lung function over shorter courses (8–10 d).

In 2008 the median predicted age of survival in the United States 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, because of 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 because of 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 FEV_1 (4–7, 10–13). Conversely, other studies have shown a significantly greater improvement in FEV_1 after inpatient treatment compared with 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 have resulted 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 d) may be as efficacious as longer courses (15 d) (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

(*Received in original form January 12, 2010; accepted in final form June 25, 2010*)

Supported by NHLBI grant HL68927 and Cystic Fibrosis Foundation funding (CUTTIN06P0 and COLLAC09A0).

Correspondence and requests for reprints should be addressed to J. Michael Collaco, M.D., 200 N. Wolfe Street, David M. Rubenstein Building, 3rd Floor, Eudowood Division of Pediatric Respiratory Sciences, Johns Hopkins University, Baltimore, MD 21287. E-mail: mcollac1@jhmi.edu

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

Am J Respir Crit Care Med Vol 182. pp 1137–1143, 2010
Originally Published in Press as DOI: 10.1164/rccm.201001-0057OC on June 25, 2010
Internet address: www.atsjournals.org

disruption of family life, costs, drug toxicity, allergic reactions, or bacterial resistance.

This study uses data from the U.S. Cystic Fibrosis Twin-Sibling Study for a large multicenter 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

A total of 1,535 individuals in 755 families were recruited through the U.S. Cystic Fibrosis Twin-Sibling Study under the oversight of the Johns Hopkins University Institutional Review Board. 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 (CFF). Informed written consent was obtained from all subjects or guardians. Pulmonary function and respiratory culture data collected by the Twin-Sibling Study were supplemented using the 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 less than or equal to 42 days in duration clinically designated for a "pulmonary exacerbation" in the CFF Patient Registry. The starting dates for treatment courses ranged from January 1, 2003, to November 7, 2007.

Lung Function

Raw 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 and lung function immediately before and after the course of antibiotics (Figure 1). Each of these measures was calculated for each exacerbation and contain data from only the time periods outlined in Figure 1. The mean ($\pm$ SD) number of pulmonary function tests (PFTs) averaged for each lung function measure were 7.1 $\pm$ 5.0, 1.3 $\pm$ 0.6, 1.3 $\pm$ 0.6, and 6.7 $\pm$ 5.1 for baseline FEV_1, pretherapy FEV_1, posttherapy FEV_1, and new baseline FEV_1, respectively. Three indices were derived to describe changes in lung function. The primary outcome of baseline change was intended to provide a measure of long-term change after 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. Because of 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 PFT data available before the start date of an exacerbation was 9.9 $\pm$ 5.7 years; only 3% of the 1,278 exacerbations used in the study had less than 1 year of baseline PFT data. For the duration of therapy analysis, normalized improvement in FEV_1 was calculated by subtracting pretherapy 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 1,535 individuals in the Twin-Sibling Study, only 1,327 had pulmonary test data available; these subjects were older (17.3 $\pm$ 9.2 yr) than the 208 subjects without PFT data (10.3 $\pm$ 20.3) ($P < 0.0001$) because younger patients may not have had exacerbations or accumulated enough lung function data to establish baselines (*see* Table E1 in the online supplement). The dataset for studying the effect of venue included 1,278 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 $\pm$ 9.5 yr) and more likely to be male (54.8%) than the 479 individuals whose PFT data was used (19.4 $\pm$ 8.3 yr, $P < 0.0001$; 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 pretherapy FEV_1 were excluded. The analysis was limited to the first 22 days of therapy because the number of FEV_1 measurements available for any particular day was fewer than 40 after Day 22 of therapy. This second dataset included 2,426 FEV_1 measurements obtained during 1,331 exacerbations in 492 subjects (*see* Figure E2). The 835 individuals with PFT data who were not used in the duration analyses were younger (16.1 $\pm$ 9.4 yr) than the 492 individuals whose PFT data was used (19.2 $\pm$ 8.4 yr; $P < 0.0001$).

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 that included time spent both in the hospital and home venue were defined as "combination" and analyzed separately. Status for *Pseudomonas aeruginosa* and *Burkholderia 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 CF 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 *t* tests; analysis of variance tests; chi-square tests; and stepwise regression analysis (generalized estimating equations: 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 less than 0.05 were dropped, excepting the variables of age, sex, and total days of therapy in any regression comparing home therapy with hospital therapy because these factors significantly differed between these two groups. Intercooled Stata 10 (StataCorp LP., College Station, TX) was used for all statistical analyses.

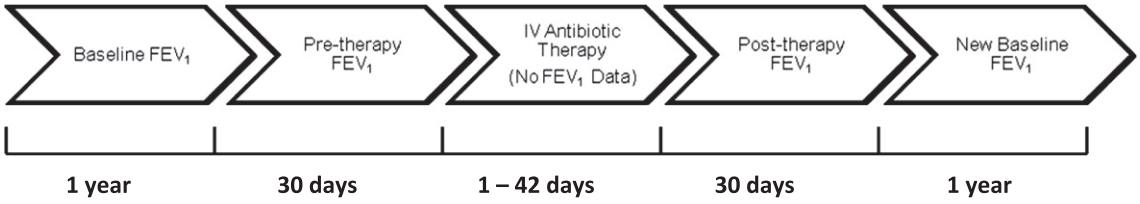
RESULTS

Demographics

Courses of antibiotic therapy within the dataset were divided into three groups (home, hospital, and combination), as described previously. Individual subjects may have received treatment in different venues on separate occasions. Groups differed significantly by sex, 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 with other groups. Average lung function before and after therapy was 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 three groups experienced a decrease in FEV_1 just before treatment for an exacerbation, generally followed by recovery to the previous baseline immediately after treatment (Figure 2). More importantly, the new baseline FEV_1 after an exacerbation was lower than the previous baseline before the exacerbation, regardless of venue ($P < 0.0001$).



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 1. Lung function measures.

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 and outpatient therapy. Using the courses of therapy from Table 1, there was no difference in baseline change after 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% confidence interval (CI), 8.2–10.2]) versus those in the home group (5 [95% CI, 3.8–6.1]); however, the hospital group had a greater initial decrease in lung function with an exacerbation (sick decline, −8.6 [95% CI, −9.5 to −7.7]) versus the home group (−5.6 [95% CI, −6.6 to −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 to −2.9]; n = 1,046) were compared with all courses treated entirely in the home setting (−3.5, [95% CI, −4.5 to −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 yr) with the outpatient therapy course preceding the inpatient course in 18 subjects. Paired *t* tests demonstrated no differences in baseline change or time until next antibiotic course.

Because the hospital and home therapy groups differed statistically by age, sex distribution, and total days of therapy (Table 1), linear regression modeling was used to adjust for these factors and 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

TABLE 1. DEMOGRAPHICS

		All	Hospital Only	Home Only	Combination: Hospital and Home	*P* Value (Hospital 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 (yr) (mean ± SD)	19.4 ± 8.3	18.2 ± 6.5	22.3 ± 9.4	20.4 ± 9.0	<0.0001
	Sex (% male)	47.4	49	34.2	44	0.01
	CFTR (% F508del homozygotes)	49.2 (n = 478)	51.2 (n = 260)	43	48.6 (n = 247)	0.35
Data by Therapy Course	Number of courses	1,278	602	232	444	—
	Age at start of therapy (yr) (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
	Pretherapy FEV_1 (mean ± SD)	60.4 ± 22.0	58.8 ± 22.0	59.5 ± 22.3	63.0 ± 21.5	0.68
	Posttherapy 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 *t* and chi-square tests.

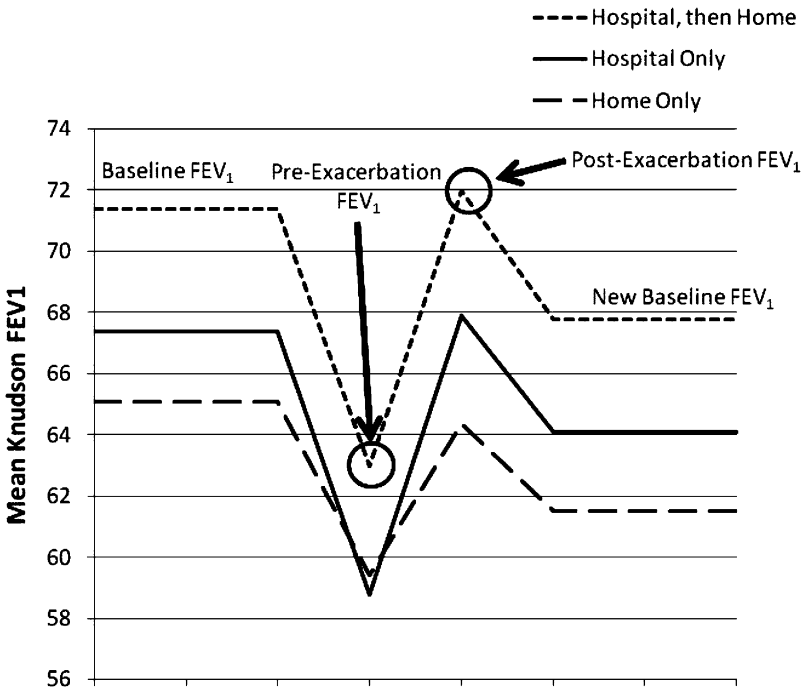


Figure 2. Mean lung function over time (based on data from Table 1). This figure provides the mean values for each measure of lung function before and after a respiratory exacerbation by venue of treatment. As can be seen, all groups experience a substantial decline in lung function with an exacerbation, followed by recovery in some cases back to the original baseline, but long-term lung function is decreased compared with the original baseline lung function. The 95% confidence intervals for all lung function measures can be found in Table E2.

regression model (Table E3), but the final model predicts that subjects with a greater decline in lung function before initiation of therapy experience a worse long-term decline after that course of therapy (sick change $P < 0.001$). This holds true even if the final model is adjusted for immediate recovery (Table E4: sick decline $P < 0.001$). This implies that patients with drastic drops in lung function should be monitored more closely after treatment, because 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 (Table E5), suggesting that location may be less important in both short- 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 with 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 (Table E6). 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

TABLE 2. CHANGE IN FEV_1: HOSPITAL VERSUS 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 and 232 home-only courses)	Sick decline = (pre-FEV_1 – baseline FEV_1)	−8.6 ± 11.2 (−9.5 to −7.7)	−5.6 ± 7.8 (−6.6 to −4.6)	0.0001
	Immediate recovery = (post-FEV_1 – pre-FEV_1)	9.2 ± 12.4 (8.2 to 10.2)	5.0 ± 9.3 (3.8 to 6.1)	<0.0001
	Baseline change = (new baseline – baseline)	−3.3 ± 8.4 (−3.9 to −2.6)	−3.5 ± 7.6 (−4.5 to −2.5)	0.69
	Days until next exacerbation: median (interquartile range)	119 (55 to 221) (n = 517)	98 (49 to 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 to −2.7)	−7.5 ± 8.3 (−10.4 to −4.5)	0.94
	Immediate recovery	7.3 ± 14.0 (2.3 to 12.3)	5.4 ± 10.0 (1.8 to 9)	0.49
	Baseline change	−4.4 ± 8.2 (−7.4 to −1.5)	−3.8 ± 6.9 (−6.3 to −1.3)	0.72
	Days until next exacerbation: median (interquartile range)	80 (37 to 204) (n = 25)	54 (44 to 138) (n = 25)	0.89

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 ($\pm$ SE) from pretherapy FEV_1 to a given day of intravenous therapy is depicted; this mean improvement has been corrected for baseline FEV_1 and 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 2,417 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 patients with CF with intravenous antibiotics remains a cornerstone in arresting or mitigating long-term decline in lung function. Our data suggest that although intravenous antibiotic therapy leads to an immediate improvement in lung function in most 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 use 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 with that administered in the hospital (4–17). The only prospective randomized study of the venue of antibiotic administration for respiratory exacerbations in patients with CF published to date found that there was no difference in lung function by therapy venue (7). Our multicenter study also did not observe any differences in short-term improvement in FEV_1 (immediate recovery) when therapy was performed at home compared with 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 yr) 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 and coworkers (14) the patients were older

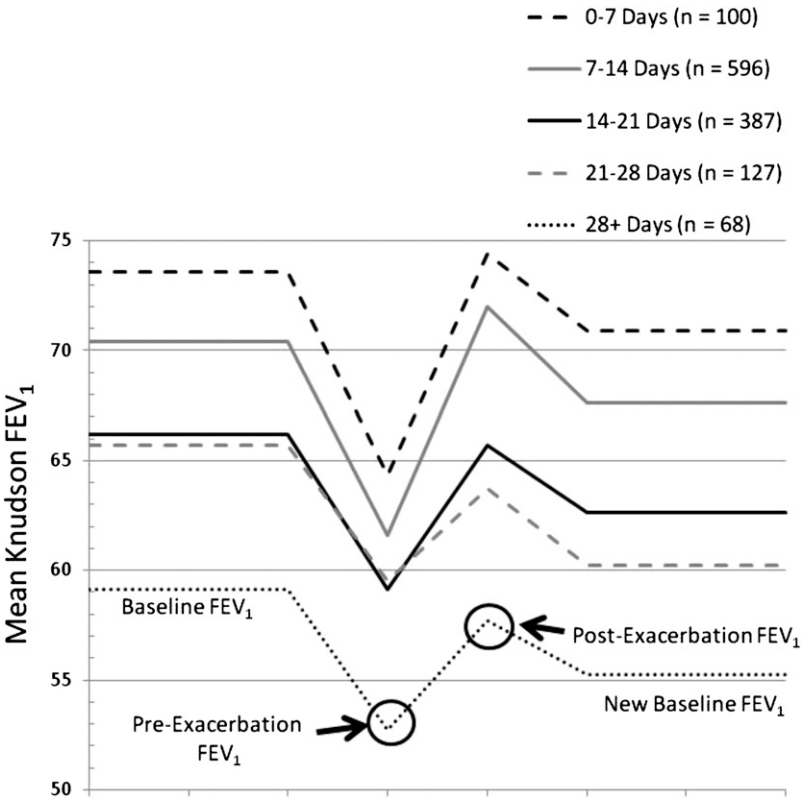


Figure 3. Change in FEV_1 by duration of therapy. This figure provides the mean values for each measure of lung function before and after a respiratory exacerbation by duration of treatment for the same population depicted in Figure 2. Subjects who receive longer courses of intravenous antibiotics tend to have worse lung function and do not recover all lost lung function immediately after a treatment course. In all groups long-term lung function is decreased compared with the original baseline lung function. The 95% confidence intervals for all lung function measures can be found in Table E2.

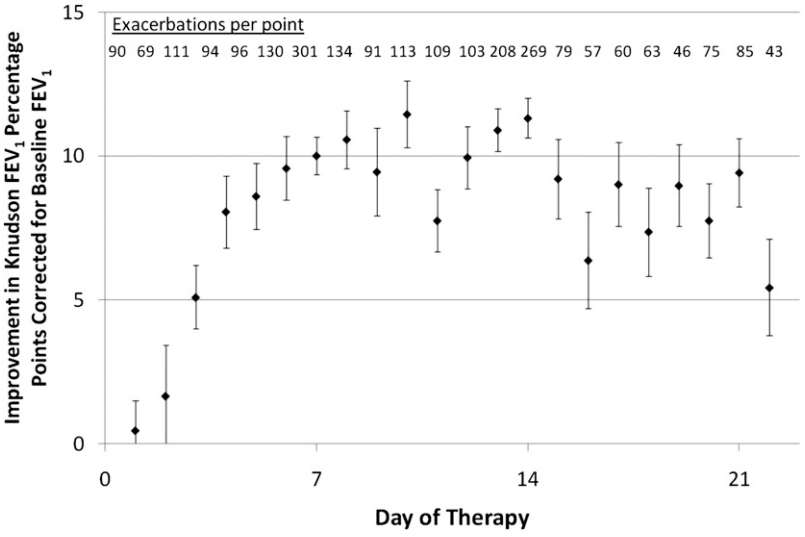


Figure 4. Mean improvement in FEV_1 by day of therapy. This figure demonstrates the SE improvement in lung function corrected and normalized (mean baseline FEV_1, 68.8%) for baseline lung function by day of intravenous therapy using pulmonary function tests obtained during therapy. The numbers above 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 because the number of FEV_1 measurements available for any particular day was fewer than 40 after Day 22 of therapy.

(mean, 26 yr, range, 16–47) and in Termoz and coworkers (17) the patients were younger (mean, 13.4 yr, 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 United States 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 most 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 and coworkers (21) noted continuous improvement in FEV_1 over 14 days of therapy. However, this study was limited to 17 subjects with more severe lung disease than our population (mean admission FEV_1, 26 $\pm$ 9%). Prospective trials to assess improvement in FEV_1 and other clinical parameters to determine optimal duration of intravenous antibiotics and risk factors for slower improvement that may require longer courses of antibiotics are needed.

Limitations to this study include the absence of an objective predetermined 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, 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 comorbidities, or families' prior experience. Also, the analyses' requirements of complete pulmonary function data before and after therapy may exclude subjects who are noncompliant with recommended follow-up, in better health and not requiring frequent PFTs, and under the age of 6 years old who cannot reliably perform PFTs. In addition, no difference between home and hospital therapy may have been observed because of 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 because 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 toward 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 before intravenous antibiotics) that could result in the possible nonsignificance 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 most improvement in lung function may occur within the first 8 to 10 days of therapy. Given the decline in baseline FEV_1 after an exacerbation, preventing exacerbations may ultimately be more important than the approach taken to treat the exacerbation.

Author Disclosure: J.M.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.M.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.R.C. has received sponsored grants from National Institutes of Health and the Cystic Fibrosis Foundation (both over $100,000). K.M.N. does not have a financial relationship with a commercial entity that has a commercial interest in the subject of this manuscript. P.J.M. has received sponsored grants (over $100,000) and advisory board fees ($10,001–$50,000) from the Cystic Fibrosis Foundation.

Acknowledgment: The authors thank the United States Cystic Fibrosis Foundation for use of the Cystic Fibrosis Foundation Patient Registry; Ase Sewall, B.S., Monica Brooks, B.S., the staff at the Patient Registry, Nulang Wang, B.S., and Sarah Ritter, B.A., for *CFTR* genotyping; Scott Blackman, M.D., Ph.D., and Patrick Sosnay, M.D., for helpful discussions; and most importantly the patients with cystic fibrosis and their families, research coordinators, nurses, and physicians who are participating in the US Cystic Fibrosis Twin and Sibling Study.

References

1. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry Annual Data Report 2008 (accessed September 13, 2010). 2008. Available from: http:/www.cff.org
2. Balaguer A, de Gonzalez DJ. Home intravenous antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* 2008;CD001917.
3. Flume PA, Mogayzel PJ Jr, Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, Marshall BC. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med* 2009; 180:802–808.
4. Donati MA, Guenette G, Auerbach H. Prospective controlled study of home and hospital therapy of cystic fibrosis pulmonary disease. *J Pediatr* 1987;111:28–33.
5. Strandvik B, Hjelte L, Malmborg AS, Widen B. Home intravenous antibiotic treatment of patients with cystic fibrosis. *Acta Paediatr* 1992;81:340–344.
6. Bramwell EC, Halpin DM, Duncan-Skingle F, Hodson ME, Geddes DM. Home treatment of patients with cystic fibrosis using the 'Intermate': the first year's experience. *J Adv Nurs* 1995;22:1063–1067.
7. Wolter JM, Bowler SD, Nolan PJ, McCormack JG. Home intravenous therapy in cystic fibrosis: a prospective randomized trial examining clinical, quality of life and cost aspects. *Eur Respir J* 1997;10:896–900.
8. Thornton J, Elliott RA, Tully MP, Dodd M, Webb AK. Clinical and economic choices in the treatment of respiratory infections in cystic fibrosis: comparing hospital and home care. *J Cyst Fibros* 2005;4:239–247.
9. Bosworth DG, Nielson DW. Effectiveness of home versus hospital care in the routine treatment of cystic fibrosis. *Pediatr Pulmonol* 1997;24:42–47.
10. Esmond G, Butler M, McCormack AM. Comparison of hospital and home intravenous antibiotic therapy in adults with cystic fibrosis. *J Clin Nurs* 2006;15:52–60.
11. Pond MN, Newport M, Joanes D, Conway SP. Home versus hospital intravenous antibiotic therapy in the treatment of young adults with cystic fibrosis. *Eur Respir J* 1994;7:1640–1644.
12. Riethmueller J, Busch A, Damm V, Ziebach R, Stern M. Home and hospital antibiotic treatment prove similarly effective in cystic fibrosis. *Infection* 2002;30:387–391.
13. Proesmans M, Heyns L, Moons P, Havermans T, De BK. Real life evaluation of intravenous antibiotic treatment in a paediatric cystic fibrosis centre: outcome of home therapy is not inferior. *Respir Med* 2009;103:244–250.
14. Thornton J, Elliott R, Tully MP, Dodd M, Webb AK. Long term clinical outcome of home and hospital intravenous antibiotic treatment in adults with cystic fibrosis. *Thorax* 2004;59:242–246.
15. Nazer D, Abdulhamid I, Thomas R, Pendleton S. Home versus hospital intravenous antibiotic therapy for acute pulmonary exacerbations in children with cystic fibrosis. *Pediatr Pulmonol* 2006;41:744–749.
16. Bradley JM, Wallace ES, Elborn JS, Howard JL, McCoy MP. An audit of the effect of intravenous antibiotic treatment on spirometric measures of pulmonary function in cystic fibrosis. *Ir J Med Sci* 1999; 168:25–28.
17. Termoz A, Touzet S, Bourdy S, Decullier E, Bouveret L, Colin C, Nove-Josserand R, Reix P, Cracowski C, Pin I, *et al.* Effectiveness of home treatment for patients with cystic fibrosis: the intravenous administration of antibiotics to treat respiratory infections. *Pediatr Pulmonol* 2008;43:908–915.
18. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, *et al.* Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003;290:2588–2598.
19. Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. *J Pediatr* 1998;132:589–595.
20. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;127:725–734.
21. Redding GJ, Restuccia R, Cotton EK, Brooks JG. Serial changes in pulmonary functions in children hospitalized with cystic fibrosis. *Am Rev Respir Dis* 1982;126:31–36.