Comparison of home and hospital intravenous antibiotic therapy for clinical outcome in patients with a pulmonary exacerbation of cystic fibrosis. Do they always need to be admitted?

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Comparison of home and hospital intravenous antibiotic therapy for clinical outcome in patients with a pulmonary exacerbation of cystic fibrosis. Do they always need to be admitted?

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ABSTRACT
INTRODUCTION: Canadian Cystic Fibrosis (CF) patients spent over 24,900 days in hospital and underwent 867 home intravenous (IV) antibiotic treatments in 2014. CF pulmonary exacerbations are treated with IV antibiotic therapy, either in hospital or at home. Yet, there is insufficient evidence to advocate for one site versus the other.

OBJECTIVES: To compare the effects of home versus hospital IV antibiotic therapy on the outcome for treatment of pulmonary exacerbation for adults with CF.

METHODS: A retrospective, chart review was conducted of patients treated for CF pulmonary exacerbation either at home or in hospital. Measures included short and long-term changes in spirometry parameters and treatment failure.

RESULTS: 91 episodes of exacerbation were included (46 treated at hospital, and 45 at home). Age, gender, home location (near a tertiary care hospital versus peripheral location) and income were similar between the two groups. There were no significant changes in FEV1% predicted (ppFEV1) between the two groups (difference of changes (95% CI) 0.49% (−3.54% to 4.53%)). Complications and readmission rates were similar. Patients without a caregiver at home and those with lower pre-treatment ppFEV1 were more likely to be treated at hospital.

CONCLUSION: Home-based intravenous antibiotic therapy is as safe and as effective as hospital-based therapy, with appropriate patient selection.

KEYWORDS
Cystic fibrosis; home intravenous therapy; home parenteral therapy; pulmonary exacerbation

INTRODUCTION
Cystic fibrosis (CF) is the most common fatal genetic disease among Canadian children and young adults.1 It mainly affects the lung resulting in abnormal airways secretions, chronic endobronchial infection and progressive airway obstruction.2 The chronic infection and inflammation of cystic fibrosis lung disease cause a progressive decline in lung function resulting in daily symptoms such as cough and sputum production. There are intermittent episodes of acute worsening of symptoms, more commonly referred to as pulmonary exacerbations.3
These exacerbations typically warrant medical intervention often with intravenous (IV) antibiotics either in hospital or at home. Cumulatively, Canadian CF patients spent over 24,900 days in hospital and underwent 867 home IV antibiotic treatments in 2014. Hospitalization of CF patients influences health cost and quality of life for patients and their families. The cost of care for patients with CF has been a major burden on patients and health care systems, especially with expensive medications such as Dornase alfa and antibiotics. The estimated cost of caring for 303 CF patients in Alberta, Canada in 1996 was CAD $2,279,801. The mean cost of care was CAD $7524 (range CAD 386–92,376)/patient. This does not take into account the cost of the new medications that have emerged since 1996. In a more recent study, the mean annual health care cost for treating CF was USD $15,571; of which 58% was accounted for by hospital inpatients. Moreover, hospitalization for pulmonary exacerbations is associated with lower health-related quality of life (HRQL) than those treated at home.

To date, there is insufficient evidence that either of the treatment sites, home or hospital, has a better outcome. We hypothesize that site of treatment does not affect the outcome for treatment of CF pulmonary exacerbation with regard to lung function and treatment failure.

**Materials and methods**

**Study design**

The study was a single-center, retrospective, chart review. All patients who had undergone IV antibiotic therapy for CF pulmonary exacerbation and treated either in our tertiary care hospital or at home between January 2010 and September 2013 were identified.

**Inclusion and exclusion criteria**

We included patients who were 17 years old and older, previously diagnosed with CF at a CF specialized centre, presenting to the outpatient clinic or to the emergency department (ED) with symptoms that were diagnosed as an acute pulmonary exacerbation of CF, and treated with intravenous antibiotics. Pulmonary exacerbation of CF was defined as worsening cough, sputum production, and shortness of breath and/or fatigue. Patients were excluded if they had undergone lung transplant, had had an acute pulmonary exacerbation of CF within the preceding 90 days or those on their first IV antibiotic therapy for CF pulmonary exacerbation. We used up to 2 episodes for a single patient.

**Data source and collection**

We reviewed paper charts and electronic health records of subjects who were admitted at the University of Alberta Hospital and patients registered at the CF clinic in Edmonton, Alberta, Canada, a CF centre providing care to Northern Alberta CF patients.

Demographic data for each subject was recorded including, age, gender, and postal code. Other background data collected were presence of caregiver, and access to outpatient coverage of specific antibiotics.

We documented symptoms and vital signs at presentation. We collected Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), absolute value and percentage predicted, at four different time periods: 2–24 weeks before the treatment (Visit 0), within 2 weeks before the treatment (Pre-treatment) (Visit 1), within 2 weeks after the end of treatment (Visit 2), and 2–24 weeks after the end of treatment (Visit 3) (Figure 1). In cases where there was more than one spirometry test done within the time window, we included the closest test to the pulmonary exacerbation event. Changes in spirometry results between visit 1 and visit 2 were defined as short-term interval treatment response, and the differences between visit 0 and visit 3 were defined as long-term interval treatment response.

Patients were assigned to the home therapy group if they spent 0–4 days in hospital and the remainder of the therapy as an out patient and to the hospital therapy group if they spent more than 4 days in hospital. Significant change in FEV1% predicted (ppFEV1) was defined as a change of 5% or more.

We collected data on the incidence of complication in both groups, including worsening/new hemoptysis, pneumothorax or any other adverse events during treatment. The incidence of another IV antibiotic therapy for the same diagnosis within 90 days after end of treatment was also documented.

We evaluated the baseline characteristics of the patients that contributed to the determination of the site of treatment. The average household income was determined based on the postal code.

**Outcome variables**

The primary outcome was change in ppFEV1 in the short and long term. The secondary outcomes were other spirometry parameters (Changes in FEV1 absolute value, FVC absolute value and percentage predicted), need for another IV antibiotic therapy within three months of the original treatment, and clinical complications such as pneumothorax, worsening/new hemoptysis and others. Recovery to baseline ppFEV1 was
defined by ppFEV1 within the 6 months after treatment that was equal or greater than 90% of the baseline ppFEV1.9

**Ethics approval**

The University of Alberta Health Research Ethics Board (Study ID M54_Pro00040030) reviewed and accepted the research protocol for this study. Individual patient consent was not obtained or required by the board.

**Statistical analysis**

Patients’ baseline characteristics, symptoms and vital signs were compared and tested for statistical significance between home and hospital. Chi-square test was used for categorical variables. We used Fisher’s exact test where chi-square test might not be valid due to small-expected counts. Non-parametric Wilcoxon-Mann-Whitney test was used for comparing age, income, Pre-treatment ppFEV1 and vital signs. Multivariable analysis was performed to assess the effect of baseline factors together with the choice of treatment site using logistic regression. We selected the factors that had univariate p-value less than 0.2 for further analysis. The final model was selected by all possible subsets regression procedure. Then best subset regression based on Bayesian information criterion (BIC) was used to select the final model. The final model is consistent with other model selection techniques e.g. best subset and stepwise based on the Akaike information criterion (AIC). Changes of ppFEV1 and other secondary outcomes were compared between home and hospital using Welch’s t-test.

**Results**

An initial list was made for the courses of IV antibiotics for CF pulmonary exacerbation and it included 264 events. Only 91 episodes met the inclusion criteria. 49% were males and median age was 27.5 years old and ranged from 22.8–40.5 years old (Table 1). Events were excluded if their charts were missing a baseline and/or pre-treatment spirometry (Visit 0 and visit 1 respectively).

A total of 173 courses were excluded from the study for the reasons of; having a history of lung transplantation (40%), enrolling two events for the same patient (30%), prior IV antibiotics in the preceding 90 days (6%), and lack of baseline and/or pre-treatment spirometry (Visit 0 and visit 1 respectively).

Forty-six episodes were enrolled in the hospital group, and forty-five in the home group. Baseline characteristics were similar between the two groups except for the presence of caregiver, and presentation encounter (Table 1).

Patients having home based therapy were more likely to have been referred by the CF clinic than emergency department (ED) compared to patients having hospital therapy (36 (80%) vs 27 (59%), p-value = 0.028)) (Table 1). There were no statistically significant differences for symptoms and vital signs at presentation (Table 2).

Median pre-treatment ppFEV1 (Visit 1) was 46% (37% to 60%) in the home group, which was significantly higher than the hospital group [30% (26% to 52%)] (P = 0.005). There was no difference between the two groups regarding the drop of FEV1 from baseline (Visit 0) to the pre-treatment one (Visit 1) (Table 3).

Presentation at the CF clinic, presence of a caregiver and pre-treatment ppFEV1 (Visit 1) were found to be statistically significant in choosing treatment site in univariate analyses. However, only presence of caregiver and pre-treatment ppFEV1 remained in the multivariable logistic regression model after performing the model selection. Presence of caregiver was

| Table 1. Baseline characteristics of the patients at presentation. |
|------------------|------------------|------------------|
|                   | Home n (%)       | Hospital n (%)   | P value |
| Age               | Median (IQR)     | Median (IQR)     |         |
| Male              | 23 (51.1)        | 22 (47.8)        | 0.754   |
| Income (in thousands) | 30.0 (23.0–40.5) | 25.0 (22.8–30.0) | 0.085   |
| Encounter ER      | 9 (20%)          | 19 (41.3%)       | 0.028   |
| Clinic            | 36 (80%)         | 27 (58.7%)       |         |
| Presence of caregiver | 27 (60.0)       | 16 (34.8)        | 0.016   |
| Comorbidities CFRD | 11 (24.4)        | 11 (23.9)        | 0.953   |
| Access to medications Insurance Self-payment | 45 (100.0) | 43 (93.5) | 0.242 |
| Difficulties in drug coverage | 0 | 3 (6.5) | 0.242 |
| House location Close to a tertiary care hospital | 23 (51.1) | 22 (47.8) | 0.754 |

Data are presented as n (%) unless otherwise specified. CFRD; Cystic Fibrosis Related Diabetes Mellitus.
associated with over a 3.5-fold increase in odds of choosing home as a treatment site, and a unit higher pre-treatment ppFEV1 was associated with a 1.05-fold increase in odds of being treated at home. The latter represents a 5% higher chance for patients with one unit (1%) lower ppFEV1 to be treated in hospital versus home (Table 4).

Our primary outcome, changes of ppFEV1 before and after treatment, was similar in both groups, in short-term and long-term treatment response (difference [95% CI] 3.57% [−1.99%, 9.13%] and 0.49% [−3.54% to 4.53%], respectively). The upper limit of two-sided 95% CI of the long-term changes was 4.53%, which is below the predefined clinically important change (5%) (Table 5). There was no statistically significant difference between proportions of patients whose ppFEV1 returned to baseline versus home (Table 4).

Additional IV antibiotic therapy within 90 days was similar in both groups (13.3% and 13.0% in home and hospital groups, respectively) (P = 0.96) and there was no difference in documented complications (such as increased hemoptysis or pneumothorax).

### Discussion

Our study shows that changes in respiratory function parameters are similar between home treatment and hospital treatment groups with regards to short-term and the long-term changes. No difference was seen in the rate of requiring more IV antibiotics in the 90 days post-treatment or complications between the two groups. There was no difference in the proportions of patients who return to baseline ppFEV1 between the two groups.

Our results are in close agreement with the study done by Collaco et al., which showed that IV antibiotic therapy administered at home is equivalent to hospital based therapy in terms of FEV1 change and interval between courses of antibiotics. Our study indicates that the same outcome would apply to the Canadian publically funded healthcare system, eliminating the potential selection bias of hospitalization cost coverage affecting treatment site selection in the United States. We were also able to assess other factors in the decision regarding the site of treatment such as caregiver support, comorbidities and presentation encounter (outpatient versus ED).

The US CF Foundation recommends against delivery of IV antibiotics at home unless resources and support equivalent to the hospital setting can be assured for the treatment of an acute exacerbation of pulmonary disease. However, there is no clear guidance regarding selection of patients who would be suitable for home antibiotic therapy.

In a Cochrane review of home vs hospital IV antibiotic therapy for CF, only one study, by Wolter et al., met the inclusion criteria. That study showed that home participants underwent fewer investigations than hospital participants and general physical activity was higher in the home group. No significant differences were found for clinical outcomes, adverse events, complications or change of intravenous lines, or time to next therapy. It was also found to be less expensive for families and the hospital.

Hodgson et al showed that outpatient parenteral antibiotic therapy (OPAT) for various infectious diseases (including CF pulmonary exacerbation) is safe and effective in children.

Home intravenous antibiotic therapy is increasingly used, because of economic pressures and the hospital bed availability.

However, the availability and the efficacy of home IV programs vary within the same country.

Factors found to significantly affect the decision of treating patients in hospital included presence of caregivers and pre-treatment ppFEV1 (Visit 1). We speculated that administration of home IV antibiotics is more challenging in the absence of caregivers due to the underlying chronic treatment burden of the disease. Pre-treatment ppFEV1 was used as a predictor of the risk of patients’ failure to recover from acute pulmonary exacerbation, which mandates closer monitoring and more aggressive treatment.

Patients who presented to the ED had similar symptoms and vital signs to those who presented to the CF clinic, suggesting that the ED group was not clinically worse. Patients from small communities in Northern Alberta had the same opportunity of being treated at home. This may indicate that, with local resources available, IV antibiotic therapy at home is feasible in communities outside of a large city.

Regarding patients who had recent IV antibiotics, they were excluded to avoid confounding by the fact that they received two courses of antibiotics within short period of time. We included up to two pulmonary exacerbation events per patient provided that the events were more than 90 days apart. However, this could be considered one of the study limitations. Furthermore, we did not collect the data regarding the time to next IV exacerbation and this is another study limitation. Patients were excluded if the recorded event was their first IV antibiotic therapy because their lack of familiarity with home IV therapy could impact the treatment outcome.

As this was a retrospective chart review, a major limitation of the study was selection bias as the treatment site was decided based on the clinician judgment rather than randomization. Other limitations of our study include the small sample size and the retrospective nature.

### Table 3. Pre-treatment FEV1 and drop in FEV1 compared between home and hospital groups.

<table>
<thead>
<tr>
<th></th>
<th>Home</th>
<th>Hospital</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment ppFEV1</td>
<td>46.00 (37.00–60.00)</td>
<td>30.00 (26.00–52.00)</td>
<td>0.005</td>
</tr>
<tr>
<td>Pre-treatment ppFEV1 absolute</td>
<td>1.78 (1.22–2.17)</td>
<td>1.16 (0.98–1.61)</td>
<td>0.003</td>
</tr>
<tr>
<td>Drop in ppFEV1, mean (SD)*</td>
<td>6.81 (9.48)</td>
<td>7.35 (7.07)</td>
<td>0.811</td>
</tr>
<tr>
<td>Drop in FEV1 absolute*</td>
<td>0.26 (0.33)</td>
<td>0.26 (0.24)</td>
<td>0.941</td>
</tr>
<tr>
<td>Return to baseline ppFEV1 at</td>
<td>82.1%</td>
<td>86.7%</td>
<td>0.745</td>
</tr>
<tr>
<td>visit 0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Drop in FEV1 is the difference between baseline FEV1 (Visit 0) and FEV1 at the treatment beginning (Visit1).

### Table 4. Adjusted odds ratios for the effects of higher pre-treatment ppFEV1 and presence of caregiver on the choice of home as a treatment site.

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment ppFEV1</td>
<td>1.05</td>
<td>(1.01, 1.09)</td>
<td>0.012</td>
</tr>
<tr>
<td>Presence of caregiver</td>
<td>3.49</td>
<td>(1.11, 10.92)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

*For every one unit (1%) higher in ppFEV1.
Table 5. Change in FEV1, FVC and FEV1/FVC.

<table>
<thead>
<tr>
<th>Change</th>
<th>Home Mean (SD)</th>
<th>Hospital Mean (SD)</th>
<th>95% CI (Hospital – Home)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term FEV1% predicted change.</td>
<td>–0.41 (9.3)</td>
<td>0.08 (8.60)</td>
<td>0.49 (–3.54 to 4.53)</td>
<td>0.808</td>
</tr>
<tr>
<td>Short-term FEV1% predicted change.</td>
<td>7.65 (11.44)</td>
<td>11.22 (8.91)</td>
<td>3.57 (–1.99, 9.13)</td>
<td>0.203</td>
</tr>
<tr>
<td>Long-term FEV1 absolute value change (L)</td>
<td>–0.002 (0.30)</td>
<td>–0.03 (0.33)</td>
<td>–0.028 (–0.18, 0.11)</td>
<td>0.667</td>
</tr>
<tr>
<td>Short-term FEV1 absolute value change (L)</td>
<td>0.29 (0.39)</td>
<td>0.47 (0.42)</td>
<td>0.18 (–0.04, 0.41)</td>
<td>0.106</td>
</tr>
<tr>
<td>Long-term FVC% predicted change.</td>
<td>0 (9.21)</td>
<td>–2.22 (11.56)</td>
<td>–2.22 (–7.02, 2.58)</td>
<td>0.359</td>
</tr>
<tr>
<td>Short-term FVC% predicted change.</td>
<td>9.60 (14.39)</td>
<td>12.57 (9.65)</td>
<td>2.97 (–3.68, 9.61)</td>
<td>0.375</td>
</tr>
<tr>
<td>Long-term FVC absolute value changes (L)</td>
<td>0.04 (0.45)</td>
<td>–0.02 (–0.51)</td>
<td>–0.06 (–0.28, 0.16)</td>
<td>0.592</td>
</tr>
<tr>
<td>Short-term FVC absolute value changes.</td>
<td>0.39 (0.55)</td>
<td>0.43 (0.46)</td>
<td>0.04 (–0.24, 0.33)</td>
<td>0.746</td>
</tr>
<tr>
<td>Long-term FEV1/FVC value changes.</td>
<td>–0.22 (5.08)</td>
<td>–1.39 (13.26)</td>
<td>–1.17 (–6.14, 3.80)</td>
<td>0.636</td>
</tr>
<tr>
<td>Short term FEV1/FVC value changes.</td>
<td>2.00 (4.86)</td>
<td>2.13 (8.60)</td>
<td>0.13 (–3.98, 4.24)</td>
<td>0.949</td>
</tr>
</tbody>
</table>

Long-term Spirometry value changes: 2nd spirometry value after treatment – spirometry value 6 months pre. Short-term Spirometry changes: 1st Spirometry value after treatment – Spirometry value at treatment beginning.

In conclusion, Home IV antibiotic therapy for acute pulmonary CF exacerbation was found to be as safe and as effective as hospital-based therapy. Presence of caregiver and lower pre-treatment ppFEV1 were factors that significantly influenced the site of treatment. Prospective studies are recommended to confirm and expand these findings.

Disclosure
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