RESEARCH NOTE

Effect of continuous-infusion antibiotic therapy on pulmonary function of patients with cystic fibrosis: A cross-sectional study [version 1; referees: awaiting peer review]

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Abstract

Background: Cystic fibrosis (CF) is associated with frequent pulmonary exacerbations which increase the mortality risk. Therefore, most CF patients are chronically colonized with respiratory pathogens, the most common being Pseudomonas aeruginosa. Multidrug-resistant organisms are a major problem in CF patients. It’s been hypothesized that continuous-infusion antipseudomonal beta-lactam therapy in CF maintains serum concentrations above the minimum inhibitory concentration of susceptible strains and is more likely than intermittent infusion to achieve optimal pharmacodynamic targets for some intermediate and resistant strains of P. aeruginosa. The most extensively studied antibiotic for continuous-infusion protocol in CF is ceftazidime, which has been shown to improve lung function (forced expiratory volume in 1 second and forced vital capacity) and to increase pulmonary exacerbation free time. There have been no studies to evaluate the cost effectiveness or impact on quality of life of continuous infusion versus intermittent infusion antibiotic therapy in patients with CF. Our study aims to investigate the effect of continuous-infusion antibiotic therapy on pulmonary function.

Methods: Cross sectional study of CF patients who were admitted to our hospital with acute pulmonary exacerbations between 1/1/2010 and 12/31/2016 and received parenteral antibiotics. We investigated the effect of use of continuous versus intermittent infusion of intravenous antibiotics on the pulmonary function (FEV1% predicted).

Results: Intermittent infusion protocol was found to have a very small advantage over continuous infusion protocol on pulmonary function; however this difference is not statistically significant (p=0.0049). The longer the duration of antibiotics, the slightly better the pulmonary function at the end of the treatment, but the difference was not significant (p=0.2543).

Conclusions: Even though we could not draw meaningful conclusions from our data, we would like bring attention to this subject because it carries an important therapeutic value for CF patients.
Keywords
Cystic Fibrosis, Pulmonary Function Test, Continuous Infusion, Intermittent Infusion, Antibiotics, Forced expiratory volume

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**Introduction**
Cystic fibrosis (CF) patients commonly suffer infections from multidrug resistant organisms, which increases their risk of treatment failure as a result of inability to meet pharmacodynamic targets (time above the minimum inhibitory concentration (T > MIC)). Continuous-infusion antibiotic therapy is believed to be more effective in achieving those targets for resistant organisms in comparison to intermittent infusion.

Studies have shown that ceftazidime, which is the most studied antibiotic for continuous infusion in CF patients, could improve forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), and reduce the frequency of pulmonary exacerbations. Continuous infusion has the potential to optimize the efficacy and safety of antimicrobial treatment during CF pulmonary exacerbations while potentially decreasing the costs of therapy.

Despite the promising results of studies comparing the two infusion protocols, there is insufficient evidence recommending the routine use of continuous infusion for patients with pulmonary exacerbations, which supports the position of the Cystic Fibrosis Foundation on this matter. There is little information regarding the impact of continuous infusion on quality of life in patients with CF. Our study aims to investigate the effect of continuous-infusion antibiotic therapy on pulmonary function.

**Methods**

**Study design and participants**
The study was reviewed and approved by the Institutional Review Board (IRB) of Virginia Commonwealth University (approval number HM20011248). The data was analyzed in its entirety by the investigators who are fully responsible for the data and conclusion.

This was a cross-sectional study. The source of data was the CF Foundation Patient Registry. We obtained data for patients registered in our institute. We randomly selected 42 CF patients who were hospitalized for acute pulmonary exacerbations between 1st January 2010 and 31st December 2016 at Virginia Commonwealth University were retrospectively reviewed. We attempted to reduce potential bias by choosing a random sample of CF patients through the simple random sampling technique. We selected a small sample size by statistical formula that assumed p value is < 0.05 and 95% confidence Interval. In addition, we compared our study size with the previously published studies.

Inclusion criteria: (1) presence of CF pulmonary exacerbation, defined as: the need for antibiotic treatment as indicated by a recent change in at least two of the following: change in sputum volume or color; increased cough; increased malaise, fatigue or lethargy; anorexia or weight loss; decrease in pulmonary function by ≥10%; radiographic changes; increased dyspnea or at the physician’s discretion. (2) Age ≥ 18 years; (3) Patient has stable vital signs; (4) Patient is not a ward of the state; (5) Suspected or proven infection; (6) The presence of a 10% decline in lung function as assessed by spirometry.

Exclusion criteria: (1) Age < 18 years; (2) Critically ill patients or patients with unstable vital signs; (3) Inmates; (4) Chronic respiratory failure (PaCO2 > 60 mm Hg as outpatient).

**Data collection**
For each patient, we collected the following variables: age, gender, ethnicity, race, body mass index, date of admission, date of discharge, antibiotic name, antibiotic infusion protocol, antibiotic start and end dates, culture data, pulmonary function test upon initiation and completion of antibiotics.

The effect of use of continuous infusion of intravenous antibiotics on pulmonary function (FEV1% predicted) was investigated.

The continuous infusion protocol has been adopted in our institute since 2013. For each patient, we collected data related to the use of intermittent infusion protocol which was the adopted protocol in our institute until 2013. From 2013 onwards, we collected data related to the use of continuous infusion protocol in order to investigate the differences in pulmonary function between the two protocols.

From each and every hospital stay (inpatient visits) for each patient, values of FEV1% predicted at the start (baseline) and end dates of the antibiotics are collected. The name of antibiotic therapies that were used, as well as the type of infusion protocol with start and end dates of each of them are also recorded.

In this study, we attempted to compare the difference in FEV1% predicted between the two infusion protocols for each individual visit. The major confounding factor is that many patients receive the intermittent-infusion at the same time as the continuous-infusion protocol.

**Data analysis**
The primary outcome of the study was a change in FEV1% predicted upon completion of antibiotic therapy. Categorical variables are reported as numbers and percent. Comparisons between groups for continuous variables were made using student t-test, while categorical variables were compared using χ² test. A nominal p-value of <0.05 was considered statistically significant. Data analysis was performed using SPSS 24.0 (IBM, Chicago, IL).

**Results**
A total of 42 patients met entry criteria and were enrolled into the study. The study cohort consisted of 21 female and 21 male patients with a mean age of 33.9 years (age range 22–61). Mean FEV1 upon initiation of antibiotics was 0.82 (FEV1/FVC ratio 43%), mean FEV1 upon completion of antibiotics was 1.9 (FEV1/FVC ratio 53%) (Table 1).

Intermittent infusion protocol was found to have a very small advantage over continuous infusion protocol on pulmonary function (based on FEV1 outputs); however, this difference is not statistically significant (p=0.0049).

The longer the duration of antibiotics, the slightly better the pulmonary function at the end of the treatment, but the difference
was not significant (p=0.2543). Patients with a history of multi-drug resistant organisms had lower pulmonary function test values and difficulty regaining their pulmonary function after treatment. As expected, patients who had higher pulmonary function test values before starting the antibiotics, had higher test values upon completion of the antibiotics, regardless of the infusion protocol (p<0.0001). When matched for other variables, older patients (age ≥ 65 years) had worse pulmonary function despite antibiotic therapy (p=0.0248). Those who had longer duration of hospital stay were noted to have a worse pulmonary function despite antibiotics (p=0.0140). African Americans had worse pulmonary function tests compared to Caucasians, but the difference was not significant (p=0.8998). Similarly, females had worse pulmonary function tests compared to males, but the difference was not significant (p=0.0930).

Discussion

The duration that β-lactams concentrations exceed the MIC for the bacteria determines its activity. Therefore, the current practice of intermittent infusion of β-lactam antibiotics may not be the optimal administration technique in CF patients. Moreover, many antibiotics have relatively short half-lives in this patient population.

There were several limitations to our study, which included the small sample size, the difficulty identifying which antibiotic protocol was adopted for each and every patient, interrupted or incomplete continuous infusion protocol and the significant difference in underlying patient demographics. We never collected or measured the beta lactam levels which is a huge limiting factor as well, as beta lactams need to be up titrated based on serum levels which we never had in this study. Without checking beta lactam levels, continuous infusion protocols seemed suboptimal to utilize so our concept of giving the same dose slowly in CF may not work.

In our opinion, although the data showed a small advantage for administration of antibiotics via intermittent infusion protocol, this finding was not statistically significant. In reality, most patients who received the continuous infusion protocol had interruptions to the protocol due to many factors, such as taking breaks for their pulmonary rehabilitation or other personal reasons. Therefore, this protocol was almost never completed as intended.

However, our conclusions are mainly based on crude associations more than statistical ones. We could not make meaningful conclusions due to the above mentioned limitations. Therefore, the study lacks generalizability.

Our study is directing attention towards a very important subject which could revolutionize the management of CF in the future. More research is really needed.

Ethical approval

The study was reviewed and approved by the Institutional Review Board (IRB) of Virginia Commonwealth University, approval number HM20011248. Consent from participants was waived by the IRB because the study is a retrospective review.

Data availability

F1000Research: Dataset 1. Raw data for ‘Effect of continuous-infusion antibiotic therapy on pulmonary function of patients with cystic fibrosis: A cross-sectional study’

Grant information

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References


Table 1. Baseline characteristics of patients.

<table>
<thead>
<tr>
<th>Race (%)</th>
<th>Mean BMI (kg/m²) ± SD</th>
<th>Gender (n)</th>
<th>Mean age (yr) ± SD</th>
<th>Mean FEV1 ± SD (start of antibiotics)</th>
<th>Mean FEV1 ± SD (end of antibiotics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian (86.8%)</td>
<td>24 ± 8.5</td>
<td>22 males, 22 females</td>
<td>33.9 ± 10.15</td>
<td>0.82 ± 0.42</td>
<td>1.9 ± 0.49</td>
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</tbody>
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