RESEARCH ARTICLE

Effect of continuous-infusion antibiotic therapy on pulmonary function of patients with cystic fibrosis: A cross-sectional study [version 1; peer review: 3 approved with reservations]

Somaya Albhaisi ¹, Fei-Pi Lin¹, Nauman Chaudary²

¹Department of Internal Medicine, Virginia Commonwealth University Medical Center, 1200 E. Broad Street, Box 980050, Richmond, Virginia, 23298, USA

²The Division of Pulmonary Disease and Critical Care Medicine, Virginia Commonwealth University Health System, 1200 E. Broad Street, Box 980050, Richmond, Virginia, 23298, USA

V1 First published: 08 Nov 2018, 7:1766
<https://doi.org/10.12688/f1000research.15598.1>
 Latest published: 08 Nov 2018, 7:1766
<https://doi.org/10.12688/f1000research.15598.1>

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 ($p=0.2543$).

Open Peer Review

Approval Status

	1	2	3
version 1
08 Nov 2018	view	view	view

1. **Martin J Walshaw**, Liverpool Heart and Chest Hospital, Liverpool, UK
2. **Zhe Hui Hoo** , University of Sheffield, Sheffield, UK
3. **Ghassan Kamel**, Saint Louis University, St Louis, USA
Edward Charbek , Saint Louis University School of Medicine, St. Louis, USA

Any reports and responses or comments on the article can be found at the end of the article.

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

Corresponding author: Somaya Albhaisi (somaya_90@hotmail.com)

Author roles: **Albhaisi S:** Conceptualization, Investigation, Methodology, Project Administration, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Lin FP:** Data Curation; **Chaudary N:** Conceptualization, Methodology, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2018 Albhaisi S *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Data associated with the article are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

How to cite this article: Albhaisi S, Lin FP and Chaudary N. **Effect of continuous-infusion antibiotic therapy on pulmonary function of patients with cystic fibrosis: A cross-sectional study [version 1; peer review: 3 approved with reservations]** F1000Research 2018, 7:1766 <https://doi.org/10.12688/f1000research.15598.1>

First published: 08 Nov 2018, 7:1766 <https://doi.org/10.12688/f1000research.15598.1>

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 ($T > MIC$))¹. 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 exacerbations². Continuous infusion has the potential to optimize the efficacy and safety of antimicrobial treatment during CF pulmonary exacerbations while potentially decreasing the costs of therapy³.

Despite the promising results of studies comparing the two infusion protocols, there is insufficient evidence recommend the routine use of continuous infusion for patients with pulmonary exacerbations, which supports the position of the Cystic Fibrosis Foundation on this matter⁴. 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 $\geq 10\%$; 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 ($PaCO_2 > 60$ 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 and 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 κ^2 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 FEV 1 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

Table 1. Baseline characteristics of patients.

Mean age (yr) $\pm$ SD	33.9 $\pm$ 10.15
Gender (n)	22 males, 22 females
Mean BMI (kg/m ²) $\pm$ SD	24 $\pm$ 8.5
Race (%)	Caucasian (86.8%), African American (13.2%)
Mean FEV1 $\pm$ SD (start of antibiotics)	0.82 $\pm$ 0.42
Mean FEV1 $\pm$ SD (end of antibiotics)	1.9 $\pm$ 0.49

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 ($p=0.0930$).

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

<http://dx.doi.org/10.5256/f1000research.15598.d222293>

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', [10.5256/f1000research.15598.d222293](https://doi.org/10.5256/f1000research.15598.d222293)⁵

Grant information

The author(s) declared that no grants were involved in supporting this work.

Acknowledgements

Many thanks to Le Kang, PhD from the Department of Biostatistics for his assistance with the data analysis.

References

- Prescott WA Jr, Gentile AE, Nagel JL, *et al.*: **Continuous-infusion antipseudomonal Beta-lactam therapy in patients with cystic fibrosis.** *P T.* 2011; **36**(11): 723–63.
[PubMed Abstract](#) | [Free Full Text](#)
- Grupper M, Kuti JL, Nicolau DP: **Continuous and Prolonged Intravenous β -Lactam Dosing: Implications for the Clinical Laboratory.** *Clin Microbiol Rev.* 2016; **29**(4): 759–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Parkins MD, Elborn JS: **Newer antibacterial agents and their potential role in cystic fibrosis pulmonary exacerbation management.** *J Antimicrob Chemother.* 2010; **65**(9): 1853–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Flume PA, Mogayzel PJ Jr, Robinson KA, *et al.*: **Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations.** *Am J Respir Crit Care Med.* 2009; **180**(9): 802–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Albhaisi S, Lin F, Chaudary N: **Dataset 1 in: Effect of continuous-infusion antibiotic therapy on pulmonary function of patients with cystic fibrosis: A cross-sectional study.** *F1000Research.* 2018.
<http://www.doi.org/10.5256/f1000research.15598.d222293>

Open Peer Review

Current Peer Review Status: ? ? ?

Version 1

Reviewer Report 26 February 2019

<https://doi.org/10.5256/f1000research.17016.r43451>

© 2019 Charbek E et al. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Ghassan Kamel

Saint Louis University, St Louis, MO, USA

Edward Charbek

Division of pulmonary, Critical Care, and Sleep Medicine, Saint Louis University School of Medicine, St. Louis, MO, USA

This is a very interesting study and raises very important point: optimal antibiotic therapy for CF exacerbations. As this is a major source of morbidity in CF patients and the introduction of antibiotics clearly improved outcomes in CF patients.

I have several comments/points to make regarding this paper:

1. What is the advantage of choosing a random sample as opposed to analysing all CF exacerbations? This is a retrospective study and larger sample would've increased the power.
2. The authors enrolled CF patients from 2010-2016 and they mentioned that continuous infusion was introduced in 2013. They did not mention what percentage of patients received continuous infusion versus intermittent.
3. It is unclear how the authors came to conclude that "the longer the duration of antibiotics, but slightly better the pulmonary function at the end of the treatment".
4. *p* value for FEV1 change was 0.0049, however, the authors reported that this was not statistically significant. The raw data do not report that actual change in FEV1.

Overall, it is understandable that the authors were unable to draw strong conclusions likely due to small sample size, however, further evaluation of the analysis maybe needed.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: COPD exacerbations, COPD, CF exacerbations, quality improvement

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have

significant reservations, as outlined above.

Reviewer Report 15 February 2019

<https://doi.org/10.5256/f1000research.17016.r43983>

© 2019 Hui Hoo Z. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Zhe Hui Hoo

School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK

Specific comments for each question on the peer review form:

1. In terms of study design, what is the justification for "choosing a random sample" (page 3) instead of analysing all available data? Also, the authors mentioned that a power calculation was done, but the results of the power calculation was not presented. The authors implied their sample size is adequate but then mentioned that "small sample size" as one of the limitations (page 4).

2. In terms of details of methods and analysis, there are several issues that should be clarified. First, what are the justification for the inclusion and exclusion criteria, in particular 10% FEV1 decline as one of the inclusion criterion and chronic respiratory failure as an one of the exclusion criterion.

Second, the authors claimed that "the continuous infusion protocol has been adopted in our institution since 2013", but "the major confounding factor is that many patients receive intermittent-infusion at the same time as the continuous-infusion protocol". Presumably this refers to beta-lactam antibiotics only. Also, presumably continuous infusion protocol was introduced in 2013 but beta-lactam may still be given via intermittent-infusion (i.e. continuous infusion was not blanketly applied). Is it not possible to restrict the analysis to people receiving only 1 type of beta-lactam as a sensitivity analysis to try understand the potential bias from the subgroup of participants that receive both intermittent and continuous beta-lactams?

Third, if the 42 participants are only a subset of those eligible, it is worth including a "CONSORT diagram" (though this is not a RCT) to help readers understand the flow from all eligible participants to participants that were finally analysed.

Fourth, what is the equation used to calculate % predicted FEV1?

Fifth, the authors claimed that "the longer the duration of antibiotics, the slightly better the pulmonary function at the end of the treatment" but what was the analysis method used to determine the correlation between treatment duration and extent of FEV1 improvement?

3. In terms of statistical analysis, the authors "attempted to compare the difference in FEV1 % predicted between the two infusion protocols and for each individual visit". Given that a

participant can have multiple courses of IV antibiotics, what is the method used to account for repeated measures within an individual? In the 'data analysis' subsection, only student t-test and chi-square test were mentioned and both these tests assume independence.

Also, for the results, it is important to display the effect size and confidence intervals, not just the p-values.

The authors claimed that FEV1 difference is not statistically significant with p-value 0.0049 (in the abstract and the text in page 3), yet p-value <0.05 was considered statistically significant. Is there a typo?

4. With regards to the source data, it would be helpful if the authors could include the key for the labels e.g. what are antibiotics Type 1 and Type 2? Also, labels such as Chest_PT and VEST were neither explained in the text nor elaborated in the data source file.

5. With regards to the conclusion drawn, it is crucial to report the difference (and confidence intervals) between group, otherwise readers are unable to judge whether there is any advantage at all favouring either the intermittent or continuous infusion group. It is also crucial to use the correct analysis method in order to justify the conclusion drawn.

Other general comments:

1. The author stated that "our study aims to investigate the effect of continuous-infusion antibiotic therapy on pulmonary function". It seems more accurate to describe the study aim as to investigate the effect on FEV1 recovery post IV treatment.

2. Some of the sentences in the introductions and discussion may benefit from being re-phrased. For example, multidrug resistant organisms "may increase" the risk of treatment failure (introduction) and I think it is hyperbolic to say that continuous beta-lactam infusion "could revolutionize the management of CF".

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cystic fibrosis, medication adherence, registry analysis (and other observational data)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 21 January 2019

<https://doi.org/10.5256/f1000research.17016.r42994>

© 2019 Walshaw M. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Martin J Walshaw

Adult Cystic Fibrosis Centre, Liverpool Heart and Chest Hospital, Liverpool, UK

This study compared continuous with intermittent beta lactam therapy for the treatment of CF exacerbations. There are theoretical reasons why continuous therapy is preferred, as the authors state.

It seems that some of their data for intermittent therapy are not contemporaneously matched with the continuous therapy, which could confound the results. Furthermore, the authors state that many of the continuous infusion admissions were interrupted - i.e. - they ended up becoming intermittent. In any event, the study showed no difference between the two methods of administration. It is incorrect to state that one method had "a very small advantage" or "slightly better pulmonary function" than the other, when in fact there was no statistical difference - by definition the outcome was the same whichever method of administration was used.

The data in the results alluding to race, age, length of stay etc. are irrelevant, since it is not expressed in relation to which type of therapy was used.

The main thrust of this paper should be that continuous and intermittent therapy are both equally efficacious in the treatment of an exacerbation.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: cystic fibrosis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research