Rescue therapy within the UK Cystic Fibrosis Registry: An exploration of predictors of intravenous antibiotic use amongst adults with CF

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ABSTRACT

Background and objective: Intravenous (i.v.) antibiotics are needed for rescue when preventative therapy fails to achieve stability among adults with cystic fibrosis (CF). Understanding the distribution of i.v. days can provide insight into the care that adults with CF need. We aim to determine the baseline characteristics that are associated with higher i.v. use, in particular to test the hypothesis that prior-year i.v. use is associated with future-year i.v. use.

Methods: This is a cross-sectional analysis of the 2013–2014 UK CF registry data. Stepwise logistic regression was performed using current-year i.v. days as the dependent variable, and demographic variables including prior-year i.v. days as the covariates. Based on these results, study sample was divided into clinically meaningful subgroups using analysis similar to tree-based method.

Results: Data were available for 4269 adults in 2013 and 4644 adults in 2014. Prior-year i.v. use was the strongest predictor for current-year i.v. use followed by forced expiratory volume in 1 s (FEV1). Adults with high prior-year i.v. use (>14 days) continued to require high levels of i.v., regardless of FEV1. Those with high prior-year i.v. use and FEV1 ≥70% had higher current-year i.v. days compared to adults with low prior-year i.v. use and FEV1 <40% (28 days, interquartile range (IQR): 11–41 days vs 14 days, IQR: 0–28 days; Mann–Whitney P-value <0.001 in 2013).

Conclusion: CF people with prior high levels of rescue often continue to need high levels of rescue even if they have good FEV1. The reasons for this require further investigations.

SUMMARY AT A GLANCE

Intravenous (i.v.) antibiotic is an important treatment option in cystic fibrosis and is also a marker of pulmonary exacerbations. Our study showed that previous-year i.v. use is a strong predictor of current-year i.v. use. This finding could help clinicians to identify people most at risk of future exacerbation.

Key words: cystic fibrosis, data interpretation, intravenous antibiotic, registry analysis, pulmonary exacerbation.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive genetic condition caused by mutations in the gene encoding the CF transmembrane regulator (CFTR) that affects around 10 000 people in the UK.1,2 CF is a multisystem condition1 but lungs are the main organ affected, with CFTR dysfunction causing abnormal airway surface liquid.1,3 People with CF are particularly susceptible to infection causing acute deterioration in lung health (i.e. pulmonary exacerbations), which leads to progressive lung damage and eventually respiratory failure.4

An important treatment option in CF is preventative inhaled therapies consisting of mucolytics and antibiotics, which have proven efficacy in reducing the frequency of exacerbations.5,6 The effectiveness of these treatments is however limited by a real-world medication adherence rates of 35–50%.7,8 Acute treatment of pulmonary exacerbations has relatively limited research evidence.9 However, the importance of intravenous (i.v.) antibiotics in managing CF is indisputable—CF centres that use less antibiotics or have higher threshold for initiating i.v. in the face of an exacerbation were
associated with people having lower lung function.10,11 Indeed, i.v. antibiotics are recommended in all the major CF guidelines to treat exacerbations.12-15 Understanding the clinical characteristics associated with i.v. antibiotics use is clinically important as it can provide insight into the care that people with CF need and the resources that are required for CF care. Exacerbation is also an important end point in CF clinical trials,16 and clinical factors associated with exacerbation could have implications for trial design.

A recent US CF Foundation Patient Registry (US CFFPR) data analysis has found that the frequency of prior-year i.v.-treated exacerbations is strongly associated with the frequency of future-year i.v.-treated exacerbations,17 even after adjustment for the other case-mix factors, for example lung function.17-19 We analysed the 2013–2014 UK CF registry data to test whether the hypothesis that prior-year i.v. use is associated with future-year i.v. use, is also generalizable to the UK CF population.

METHODS

This is a cross-sectional analysis using the UK CF registry data for 2013–2014 from 28 UK adult CF centres. National Health Service (NHS) research ethics approval (Huntingdon Research Ethics Committee 07/Q0104/2) was granted for the UK CF Registry. Under the terms of the NHS ethics approval, the UK CF Trust steering committee approved this study.

People with lung transplantation and those on ivacaftor were excluded as both treatments have transformative impacts on health outcomes,20,21 such that their exacerbation is also an important end point in CF clinical trials,16 and clinical factors associated with exacerbation could have implications for trial design.

Statistical analysis

Analyses were performed using SPSS v22 (IBM Corp, Armonk, NY, USA). Data for 2013 and 2014 were analysed separately to determine the consistency of any observations. The analysis consisted of two stages. First, logistic regression was performed to identify the order of the strength of association between the demographic and clinical variables with the current-year i.v. use. Based on these results, the study sample was divided into clinically meaningful subgroups using analysis similar to tree-based method26 for comparison of current-year i.v. use between the subgroups. Logistic regression was performed using current-year i.v. days (≤14 days vs >14 days) as the dependent variable. 14-Day was selected as the cut-off since mean and median duration of each i.v. course in 2013 and 2014 was 14 days. The duration of a ‘standard’ i.v. course to treat an exacerbation is usually 14 days,12,15 and people with ≥2 exacerbations per year (i.e. time between exacerbation <6 months19) have the most rapid FEV1 decline.22 Age, gender, CF centre (as a categorical variable), pancreatic status, CF-related diabetes, intermittent P. aeruginosa (yes/no), chronic P. aeruginosa (yes/no), BMI, %FEV1 and prior-year i.v. days (as a continuous variable) were the covariates. For this procedure, forward stepwise conditional analysis (probability for entry 0.05; probability for removal 0.10) was performed in a binary logistic regression model. The procedure began by identifying the covariate that was most strongly associated with current-year i.v. use. The next strongest associated covariate was then selected after controlling for the first covariate. This continued until no further statistically significant covariates can be added to the model. Stepwise regression allows a relatively parsimonious model to be built even when several correlated covariates are present,20,25 but it is essentially an exploratory analysis because it can lead to inflated Type I errors.30,31 Therefore, the results from the stepwise logistic regression were subjected to a further analysis similar to tree-based method to test the hypothesis that prior-year i.v. use is associated with future-year i.v. use. Tree-based method is an efficient approach to understand the impact of risk factors for a condition where many potential confounders exist.24 For this analysis, the covariate most strongly associated with current-year i.v. use as identified by stepwise logistic regression was used for the first ‘layer’ division of the study sample. Then, a further ‘layer’ of division for each generated subgroup was carried out using the next strongest associated covariate, and so on. For continuous covariates, clinical meaningful cut-off points were used to divide the cohort instead of data-driven optimal cut-off points to avoid overfitting.32 For %FEV1, internationally accepted categories (<40%, 40–69.9% and ≥70%) were used as these categories are also applicable to the UK CF registry data.33 Prior-year i.v. days were categorized into ≤14 days versus >14 days, similar to current-year i.v. days. The current-year i.v. days, as a continuous variable, were compared between subgroups at each ‘layer’ division of the study sample.
of the division using Mann–Whitney test or Jonckheere–Terpstra test depending on the number of subgroups, due to the non-normal distribution of i.v. days. Jonckheere–Terpstra test is a generalization of the Mann–Whitney test for more than two ordered groups.

The analyses included those without any pulmonary exacerbations needing i.v. antibiotics \((n = 1847, 43.3% \text{ of the sample for 2013}; n = 2037, 43.9% \text{ of the sample for 2014})\) to obtain a more representative understanding of the adult CF population in the UK. \(P\)-value <0.05 was considered to be statistically significant. Complete case approach was used as the extent of missing data (summarized in Fig. 1) was small. There were >1500 people with >14 days i.v. days for each year, which is more than adequate power for nine covariates in a binary logistic regression model.34 The study sample was also considerably larger than previous studies looking at factors associated with exacerbations18,19 (except the recent US CFPR analysis), which should allow adequate power for hypothesis testing between the different subgroups.

RESULTS

A total of 4269 adults were included in the analysis for 2013 and 4644 for 2014, with 4874 study subjects in total across both years. In total, 103 453 i.v. days were used in 2013 and 111 981 i.v. days were used in 2014. Figure 1 summarizes the numbers of adults excluded and missing data. Baseline demographics stratified according to previous i.v. days was summarized in Table 1. Those with previous-year i.v. use >14 days had lower \(\text{FEV}_1\) and higher current-year i.v. use for both 2013 and 2014.

Graphs displaying the relationships between continuous covariates (age, BMI, \%\text{FEV}_1\) and prior-year i.v. days) with current-year i.v. days are available in Appendix S1 (Supplementary Information). Contingency tables for all covariates are available in Appendix S2 (Supplementary Information).

For both 2013 and 2014, prior-year i.v. use was the strongest predictor for current-year i.v. use, followed by \(\text{FEV}_1\). Other covariates such as CF centre and pancreatic status were also associated with i.v. use, but the relationship was weaker and less consistent (Wald statistic <100) once prior-year i.v. use and \(\text{FEV}_1\) had been taken into account (final model summarized in Table 2). Prior-year i.v. use and \(\text{FEV}_1\) remained the strongest predictors for current-year i.v. use in various sensitivity analyses (Appendix S3, Supplementary Information).

Therefore, the cohort was divided into two groups based on prior-year i.v. use (≤14 days and >14 days)

![Figure 1](image-url)  
**Figure 1** Summary of the number of adults included in the analyses and details regarding missing data. \(^1\) Cystic fibrosis (CF)-related diabetes (CFRD) data are collected by the UK CF registry with only a check-box for ‘CFRD present’. Therefore, if data are not available, it is assumed the person has no CFRD. It is therefore difficult to distinguish missing data from ‘no CFRD’ and hence missing data = 0. \(^2\)Data for pancreatic replacement therapy (PERT) use were obtained. People on PERT were considered ‘pancreatic insufficient’. People not on PERT were considered ‘pancreatic sufficient’. PERT use documented as ‘unknown’ is considered as missing data. \(^3\)P. aeruginosa status is collected by the UK CF registry with check-boxes for ‘chronic’ and ‘intermittent’. Therefore, if data are not available, it is assumed the person has no P. aeruginosa. It is therefore difficult to distinguish missing data from ‘no P. aeruginosa’ and hence missing data = 0.
Table 1  Current year demographic and clinical characteristics stratified by prior-year i.v. days

<table>
<thead>
<tr>
<th>Demographics and clinical characteristics</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior-year i.v. days ≤ 14(^{1})</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 2433</td>
<td>n = 1640</td>
<td>n = 4269</td>
</tr>
<tr>
<td>Age (years) median (IQR)</td>
<td>28 (22–37)</td>
<td>27 (22–33)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>995 (40.9)</td>
<td>849 (51.8)</td>
</tr>
<tr>
<td>Pancreatic insufficient (%)</td>
<td>1858 (77.5)</td>
<td>1487 (92.0)</td>
</tr>
<tr>
<td>CF-related diabetes (%)</td>
<td>568 (23.3)</td>
<td>760 (46.3)</td>
</tr>
<tr>
<td>% Predicted FEV(_1), mean (SD)</td>
<td>73.0 (23.4)</td>
<td>51.8 (21.1)</td>
</tr>
<tr>
<td>Current-year i.v. days, median (IQR)</td>
<td>0 (0–14)</td>
<td>42 (16–67)</td>
</tr>
<tr>
<td><strong>Prior-year i.v. days &gt; 14(^{1})</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 1600</td>
<td>n = 2586</td>
<td>n = 1675</td>
</tr>
<tr>
<td>Age (years) median (IQR)</td>
<td>28 (22–37)</td>
<td>27 (22–33)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>1066 (41.2)</td>
<td>877 (52.4)</td>
</tr>
<tr>
<td>Pancreatic insufficient (%)</td>
<td>1967 (77.0)</td>
<td>1526 (91.8)</td>
</tr>
<tr>
<td>CF-related diabetes (%)</td>
<td>620 (24.0)</td>
<td>810 (48.4)</td>
</tr>
<tr>
<td>% Predicted FEV(_1), mean (SD)</td>
<td>71.7 (22.9)</td>
<td>55.0 (24.8)</td>
</tr>
<tr>
<td>Current-year i.v. days, median (IQR)</td>
<td>14 (0–35)</td>
<td>14 (0–40)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 4269</td>
<td>n = 4644</td>
<td>n = 4644</td>
</tr>
<tr>
<td>Age (years) median (IQR)</td>
<td>28 (22–37)</td>
<td>27 (22–33)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>1066 (41.2)</td>
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<td>% Predicted FEV(_1), mean (SD)</td>
<td>71.7 (22.9)</td>
<td>55.0 (24.8)</td>
</tr>
<tr>
<td>Current-year i.v. days, median (IQR)</td>
<td>14 (0–35)</td>
<td>14 (0–40)</td>
</tr>
</tbody>
</table>

\(^{1}\)As shown in Figure 1, there were 196 missing data for prior-year i.v. days in 2013.

\(^{1}\)As shown in Figure 1, there were 383 missing data for prior-year i.v. days in 2014.

CF, cystic fibrosis; FEV\(_1\), forced expiratory volume in 1 s; IQR, interquartile range.

Table 2  Summary of the output from the final binary logistic regression model which include all nine covariates listed

<table>
<thead>
<tr>
<th>Covariates</th>
<th>2013</th>
<th></th>
<th>2014</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wald statistic</td>
<td>P-value</td>
<td>Adjusted odds ratio (95% CI)</td>
<td>Wald statistic</td>
<td>P-value</td>
</tr>
<tr>
<td>Prior-year i.v. days</td>
<td>449.5</td>
<td>&lt;0.001</td>
<td>1.06 (1.05–1.06)</td>
<td>458.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Predicted FEV(_1)</td>
<td>140.1</td>
<td>&lt;0.001</td>
<td>0.97 (0.97–0.98)</td>
<td>172.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CF centre</td>
<td>90.3</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>32.5</td>
</tr>
<tr>
<td>Pancreatic insufficient</td>
<td>9.6</td>
<td>&lt;0.001</td>
<td>1.59 (1.19–2.13)</td>
<td>Female</td>
<td>32.4</td>
</tr>
<tr>
<td>Chronic P. aeruginosa</td>
<td>21.9</td>
<td>&lt;0.001</td>
<td>1.57 (1.30–1.89)</td>
<td>Chronic P. aeruginosa</td>
<td>30.9</td>
</tr>
<tr>
<td>Female</td>
<td>15.9</td>
<td>&lt;0.001</td>
<td>1.44 (1.20–1.71)</td>
<td>CF centre</td>
<td>67.6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>17.6</td>
<td>&lt;0.001</td>
<td>0.98 (0.97–0.99)</td>
<td>Intermittent</td>
<td>4.2</td>
</tr>
<tr>
<td>CF-related diabetes</td>
<td>13.6</td>
<td>&lt;0.001</td>
<td>1.44 (1.19–1.75)</td>
<td><em>P. aeruginosa</em></td>
<td></td>
</tr>
</tbody>
</table>

CF, cystic fibrosis; FEV\(_1\), forced expiratory volume in 1 s.

DISCUSSION

This study found that adults with high prior-year i.v. use (>14 days) and low FEV\(_1\) (<40%) required the most i.v. among the six different clinical subgroups. In 2013, this group consisted 13.4% of the population but consumed 38.7% of i.v. days. Prior-year i.v. use was a much stronger predictor of current-year i.v. use compared to FEV\(_1\), such that those with high prior-year i.v. use and high FEV\(_1\) (≥70%) still used more i.v. therapies compared to those with low prior-year i.v. use (≤14 days) and low FEV\(_1\). The 2013 results were consistent with 2014 results, suggesting that chance is extremely unlikely to explain these results.

The finding that prior-year i.v. use was the strongest independent predictor of current-year i.v. use is consistent with the recent US CFFPR analysis.\(^{17}\) Whilst we acknowledge the limitations of retrospective observational registry-based analyses that have been previously discussed,\(^{17,35}\) the consistency and magnitude of the

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Figure 2  Tree-based diagram for 2013 to summarize current-year i.v. days according to the different clinical subgroups. CF, cystic fibrosis; FEV₁, forced expiratory volume in 1 s; IQR, interquartile range.

Figure 3  Tree-based diagram for 2014 to summarize current-year i.v. days according to the different clinical subgroups. CF, cystic fibrosis; FEV₁, forced expiratory volume in 1 s; IQR, interquartile range.
finding would suggest a genuine signal. The implications of this finding for clinical trials had also been discussed in detail—stratification of subject randomization by prior-year i.v. use would be helpful to balance the baseline risk of pulmonary exacerbation. In fact, our randomized control trial to evaluate a complex self-care intervention used this strategy for randomization.

This finding also has other important clinical implications and could suggest possible differences in management strategies. Management of CF can be broadly dichotomized into ‘rescue’ therapy with i.v. antibiotics to treat pulmonary exacerbations and ‘prevention’ with inhaled therapies to minimize the risk of exacerbations. Whilst exacerbations may be stochastic events, the frequency and severity of exacerbations over a given period in a person with CF will be influenced by their clinical characteristics, environmental exposures and medical treatments. Given the efficacy of preventative inhaled therapies in reducing the frequency of exacerbations, a possible explanation for high i.v. use would be the reliance on rescue therapies to compensate for insufficient utilization of preventative therapies.

Prior-year i.v. use could also guide clinical strategy in managing CF. Insufficient utilization of preventative therapy could be due to low adherence, as median adherence with inhaled therapies in the real world is only 35–50%. Therefore, it is important to obtain objective adherence data wherever possible when assessing an adult with CF, especially if i.v. use is disproportionately high in relation to FEV1.

If objective nebulizer adherence is satisfactory, another cause for insufficient utilization of preventative therapy to consider is ‘therapeutic inertia’. Therapeutic inertia refers to the under-prescription of efficacious treatments. In CF, the prescription of inhaled therapies has increased since mid 1990s. Adherence rates to international prescribing guidelines now exceed 90% for some specialist CF centres. If i.v. requirement is still disproportionately high but objective adherence is high, and no obvious complications are found, escalation of preventative therapies should be considered. An example would be the initiation of inhaled antibiotic treatment for someone who is only on inhaled mucolytics. The detection of P. aeruginosa infection would typically prompt the prescription of inhaled antibiotics. However, there may be merit in using long-term inhaled antibiotics, even when P. aeruginosa is not detected, if there is a history of frequent exacerbations. This is a strategy that has some evidence of success in non-CF bronchiectasis.

Our finding highlights potential limitations of FEV1 as a marker of lung health. Low FEV1 is a known poor prognostic marker in CF and is strongly associated with mortality. FEV1 trend is therefore a commonly used primary end point in CF clinical trials and an important parameter measured during annual reviews as a marker of lung health for adults with CF. However, as the health of people with CF improved over time, the sensitivity of FEV1 as a marker of lung health decreases. This study found a group of people with high i.v. use year on year, yet who maintained relatively good lung function (FEV1 > 70%). It may be possible to initially fend off FEV1 decline despite frequent exacerbations by simply relying on prompt and aggressive rescue i.v. treatments. Such strategy is likely to result in wild fluctuations of FEV1, with high FEV1 post i.v. treatment not sustained due to lack of preventative treatments. A trend of declining FEV1 tends to be preceded by increased FEV1 variability; hence, FEV1 variability is a more sensitive marker of lung health.

In conclusion, exacerbations as indicated by i.v. use are clinically important events in CF with long-term impact on morbidity and mortality. Prevention of exacerbations is a priority due to the risk of FEV1 decline and lung damage even with intensive i.v. antibiotics, hence the importance of understanding the predictors of frequent exacerbations. This UK CF registry analysis used i.v. days as a marker of the frequency and severity of exacerbations, and found that current-year i.v. use is most strongly associated with prior-year i.v. use. A recent US CFFPR data analysis also found similar results. That means those with history of frequent exacerbations continue to remain most at risk for future exacerbations, even with good FEV1. Inadequate utilization of preventative inhaled therapies may be one of the reasons for this reliance on rescue therapies. Therefore, high i.v. use should prompt clinicians to assess both the adherence rate and the prescribed inhaled therapies regime.

Acknowledgements

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Disclosure statement

Part of the analysis in this paper has been presented as an oral presentation in the 2016 European Cystic Fibrosis Society Conference. The abstract is published in the Journal of Cystic Fibrosis 2016, Vol 15, Suppl 1, entitled Rescue therapy within the UK CF registry: an exploration of the predictors of i.v. antibiotic use amongst adults with CF.

REFERENCES

Predictors of i.v. antibiotic use in CF


**Supplementary Information**

Additional supplementary information can be accessed via the html version of this article at the publisher’s website.

**Appendix S1** The relationships between age, BMI, % forced expiratory volume in 1 s and prior-year i.v. days with current-year i.v. days for 2013 and 2014.

**Appendix S2** A contingency table showing the distribution of covariates according to current-year i.v. days.

**Appendix S3** Sensitivity analyses using number of i.v. courses (instead of i.v. days) as the dependent variable in a logistic regression model and using ordinal regression models to explore different cut-off points for i.v. courses and i.v. days.

**Appendix S4** Sensitivity analyses using number of i.v. courses (instead of i.v. days) and different cut-off points to generate the clinical subgroups.