
Article:
Hoo, Z.H. orcid.org/0000-0002-7067-3783, Campbell, M.J. orcid.org/0000-0003-3529-2739, Curley, R. et al. (2 more authors) (2018) Do cystic fibrosis centres with the lowest FEV1 still use the least amount of intravenous antibiotics? A registry-based comparison of intravenous antibiotic use among adult CF centres in the UK. Journal of Cystic Fibrosis, 17 (3). pp. 360-367. ISSN 1569-1993

https://doi.org/10.1016/j.jcf.2017.10.005

Title: DO CYSTIC FIBROSIS CENTRES WITH THE LOWEST FEV_1 STILL USE THE LEAST AMOUNT OF INTRAVENOUS ANTIBIOTICS? A REGISTRY-BASED COMPARISON OF INTRAVENOUS ANTIBIOTIC USE AMONG ADULT CF CENTRES IN THE UK

Short title: CF centre-level IV antibiotic use in the UK

Author names (surnames are underlined) and affiliations:

Zhe Hui Hoo[1,2] z.hoo@sheffield.ac.uk
Room 1.03, Innovation Centre, 217, Portobello, Sheffield S1 4DP, United Kingdom.

Michael J. Campbell[1] m.j.campbell@sheffield.ac.uk
ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, United Kingdom

Rachael Curley[2,1] rachael.curley@sth.nhs.uk
Sheffield Adult Cystic Fibrosis Centre, Brearley Outpatient, Northern General Hospital, Herries Road, Sheffield S5 7AU, United Kingdom.

Stephen J. Walters[1] s.j.walters@sheffield.ac.uk
ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, United Kingdom

Martin J. Wildman[2,1] martin.wildman@sth.nhs.uk
Sheffield Adult Cystic Fibrosis Centre, Brearley Outpatient, Northern General Hospital, Herries Road, Sheffield S5 7AU, United Kingdom.

[1] School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK
[2] Sheffield Adult CF Centre, Northern General Hospital, Sheffield, UK

Corresponding author:
Zhe Hui Hoo.
Room 1.03, Innovation Centre, 217, Portobello, Sheffield S1 4DP, United Kingdom.
Email: z.hoo@sheffield.ac.uk

ABSTRACT

Background

The Epidemiologic Study of Cystic Fibrosis using 1995-1996 and 2003-2005 data found that CF centres with lowest FEV_1 tended to use fewer intravenous antibiotics. We repeated the analyses using 2013-2014 UK CF registry data to determine if this was still the case.

Methods

Analysing data for 2013 and 2014 separately, 28 adult CF centres were ranked according to median % age-adjusted FEV_1. The top 7 centres were placed in the 'upper quarter' (best FEV_1), the bottom 7 centres in 'lower quarter' (lowest FEV_1), and the rest in 'middle half'. IV use was stratified according to $\%FEV_1$, then compared between the three groups.

Results

Centres in the 'upper quarter' and 'middle half' used significantly more IV antibiotics compared to centres in the 'lower quarter' (van Elteren test p-value <0.001). Regression analyses showed that people with CF attending centres in the 'upper quarter' or 'middle half' are 30-50% more likely to receive at least one IV course per year compared to people attending centres in the 'lower quarter'.

Conclusions

CF centres with lowest FEV_1 are still distinguished by lower use of intravenous antibiotics.

KEYWORDS

Cystic fibrosis

Clinical epidemiology

Registry analysis

Intravenous antibiotic

Pulmonary exacerbation

1. INTRODUCTION

CF is an archetypal long-term condition in which treatment involves both reactive, disruptive and expensive hospital based rescue using intravenous (IV) antibiotics and community based prevention using inhaled therapies. IV antibiotics to treat pulmonary exacerbations are needed as rescue when preventive therapy fails to achieve stability.

Intensive IV use, in the form of scheduled IV courses not primarily driven by symptoms, was first noted to be beneficial in a Danish observational study [1]. 5-year survival improved from 54% in 1971-75 to 82% in 1976-80 following routine IV administration every 3-4 months for people with chronic Pseudomonas [1]. Intensive IV use gained further acceptance after the Epidemiologic Study of Cystic Fibrosis (ESCF) using 1995-1996 data showed that North American centres with higher FEV_1 also have higher IV use [2]. Indeed, regular IV use became such an ingrained practice that a randomised control trial in late 1990's aiming to compare routine (3-monthly) vs elective (only when symptomatic) IV found similar IV usage in both arms [3].

Preventive inhaled therapies (antibiotics and mucolytics) became available from 1990's onwards, and prescriptions of these increased from 1995-2005 [4,5]. Regular use of preventive therapy might be expected to reduce the need for IV antibiotics, given that randomised clinical trials of inhaled therapies typically demonstrates a reduction in exacerbation [6,7]. However, analysis of the 2003-2005 ESCF data found that centres with higher FEV_1 continued to use more IV [8].

Intensive IV use is not without its drawbacks. As CF survival continues to improve [9,10], increased cumulative exposure to high doses of IV antibiotics could increase the frequency and severity of systemic side-effects, particularly renal failure [11,12]. Since 2005, newer classes of inhaled therapies have been introduced and prescriptions of these have also increased [13]. In this decade, the plethora of efficacious inhaled therapies [6,7] might be expected to allow CF centres to move away from dependence on IV antibiotics. This might mean that centres using less IV may no longer have the lowest FEV_1. However, such a desirable change cannot be taken for granted because the mean composite medication possession ratio (MPR) data from a US study of 3287 people with CF suggests <50% of preventive therapies were collected [14]. UK data suggest that median objectively measured adherence to inhaled therapies among adults is only 36% [15].

We therefore repeated the ESCF analysis using the 2013-2014 UK CF registry data to determine whether low IV use continues to be associated with centres with lower FEV_1. We hypothesised that UK specialist adult CF centres with lower FEV_1 are no longer distinguished by lower IV use because efficacious inhaled therapies are increasingly available.

2. METHODS

This cross-sectional analysis using the 2013-2014 UK CF registry data involved people aged ≥16 years with CF receiving care at all 28 UK specialist adult centres. People with lung transplantation

or on ivacaftor were excluded since both treatments have transformative effects on FEV_1 [16,17], such that their FEV_1 no longer represent that of a typical adult with CF.

2.1. Data

Data obtained include demographics (age, gender, CF centre identifier), body mass index (BMI, in kg/m^2), annual review FEV_1 (in % predicted, calculated with Knudson equation) [18], annual IV antibiotic use (number of IV courses and total IV days per year) and prescription of preventive therapies (inhaled antibiotics, inhaled mucolytics and long-term oral macrolide).

Data were collected during annual reviews from January 2013 to December 2014. Data for best annual FEV_1, *P. aeruginosa* status and pancreatic status were also obtained for analyses detailed in Appendices B, C, E and F.

2.2. Statistical methods

Analyses were performed using SPSS v22 (IBM Corp) and R v3.3.0 (www.r-project.org). Data for 2013 and 2014 were analysed separately. For each year, centres were ranked according to their median % age-adjusted FEV_1, then divided into three groups ('upper quarter', 'middle half', 'lower quarter'). IV use was then stratified according to $\%FEV_1$ for between-group comparison.

CF specific age-adjustment for $\%FEV_1$ were performed using a generalised linear model approach to create an adjusted FEV_1 taking account of FEV_1 decline in CF populations [19]. For both 2013 and 2014, the cohort was divided into 10 age groups with similar numbers of study subjects in each decile. The 'predicted' $\%FEV_1$ for each age decile was calculated using a linear model (the resultant actual age adjustment was non-linear; see Appendix A). The % age-adjusted FEV_1 is the actual $\%FEV_1$ divided by the predicted $\%FEV_1$ for people of this age with CF. Therefore, % age-adjusted FEV_1 >100% represents better than expected $\%FEV_1$ for a person's age, whereas % age-adjusted FEV_1 <100% represents worse than expected $\%FEV_1$ for a person's age. The median % age-adjusted FEV_1 for each centre was calculated to rank the centres from highest to lowest. The centres were then divided into 3 groups. The 'upper quarter' consisted of the 7 centres with the highest median % age-adjusted FEV_1, the 'lower quarter' consisted of the 7 centres with the lowest median % age-adjusted FEV_1 whilst the 'middle half' consisted of the remaining centres in the middle (n=13 for 2013, n=14 for 2014). The discrepancy between the number of centres in 2013 and 2014 was due to one of the centres not providing any annual review data in 2013. Descriptive statistics of baseline characteristics were obtained for each group. The consistency of centre rankings from 2013-2014 was assessed with Spearman's rho.

For comparison of the annual IV use between the three groups, adults in each group were pooled and stratified according to $\%FEV_1$ (<40%, 40-69.9%, ≥70%) to allow comparison among cohorts of adults with similar lung health and to control for case-mix confounding factors. These internationally used $\%FEV_1$ categories have been shown to be applicable to the UK CF registry data [20]. Stratified Wilcoxon rank sum test was used to compare IV use between 'upper quarter' vs 'lower quarter', 'upper quarter' vs 'middle half' and 'middle half' vs 'lower quarter', with

Bonferroni correction applied for multiple comparisons. Percentage of people prescribed at least one IV course per year were similarly compared, using the Cochran–Mantel–Haenszel test. Data on the prescription of preventive therapies, including inhaled antibiotics, inhaled mucolytics and long-term macrolide were also analysed in a similar method to IV use, to determine if there are other differences in the process of care that could influence FEV_1. Cochran–Mantel–Haenszel test was used to compare these prescription data, which were available as binary variables (prescribed vs not prescribed). P-value <0.05 after Bonferroni correction was considered statistically significant.

The methods described were similar to the ESCF methods [2], with minor differences. The ESCF analysis involved both paediatric and adult centres. We restricted the analysis to adult centres because we wanted to compare care in different centres, and the shared care arrangements in paediatrics made centre comparisons problematic [21]. The ESCF analysed everyone aged ≥18 years as a single cohort without $\%FEV_1$ adjustment, whereas we adjusted $\%FEV_1$ for age in this analysis due to significant between-centre age differences in the UK [22]. ESCF used four FEV_1 categories for stratification (FEV_1 ≥100% was included), whereas we used three categories since children who tend to have FEV_1 ≥100% were excluded from this analysis. ESCF aggregated results over a 2-year period whereas we analysed the data year-by-year to determine the consistency of any observed differences. ESCF compared 'upper' vs 'lower' quarter, whereas we included the 'middle half' to understand the pattern of IV use across all centres.

The number of adults in the 'upper' and 'lower' quarters of this analysis is larger than the adult population in the ESCF study, which should allow for adequate power to detect differences in IV use across the three groups of centres.

2.3. Further explanation of the statistical method

Since this analysis set out to allow comparison of the 2013-2014 epoch with the original 1995-1996 ESCF epoch where inhaled therapies were less widely used, our reported analysis in the main paper mirrors the ESCF methods [2]. An alternative method to control for confounding is regression modelling. As a sensitivity analysis, we have performed regression analysis for IV days and number of IV courses; adjusting for gender, age, pancreatic status, $\%FEV_1$ and *P. aeruginosa* status using a similar Generalised Linear Model (GLM) approach as described in Appendix A. This involved calculating the predicted IV days and number of IV courses for each study subject by fitting gender, age, pancreatic status, $\%FEV_1$ and *P. aeruginosa* status as categorical variables in a linear model. The case-mix adjusted IV days and IV courses for each study subject were then determined, and compared between all three groups of specialist adult CF centres ('upper quarter', 'middle half', 'lower quarter'). We also used a binary logistic model to compare the proportion of people prescribed at least one course of IV antibiotics per year among all three groups of specialist adult CF centres, adjusting for the same set of categorical variables. Further explanation of these regression analyses and results are presented in Appendix B.

We did not use a multi-level model to compare IV use of each CF centre because this approach is limited by the number of adults in smaller centres and potential systematic bias in annual review FEV_1 data (further explanation in Appendix C).

3. RESULTS

4269 adults were included for 2013, and 4644 for 2014. Appendix D summarises the numbers of adults excluded and missing data. Centre ranking was consistent from 2013-2014, with Spearman's rho of 0.71.

Table 1 summarises the characteristics of study subjects. Since centres were ranked according to % age-adjusted FEV_1, the substantial between group differences in % age-adjusted FEV_1 are as expected. Some of the centres in the 'lower quarter' have adults that were slightly older, but this was likely due to those CF centres being established earlier rather than actual differences in survival. The $\%FEV_1$ differences between the three groups of centres were also disproportionate to age differences. As shown in Table 2, centres in the 'upper quarter' have superior $\%FEV_1$ age-for-age, indicating these centres have the best outcomes. In particular, FEV_1 at the age of 20 years has been suggested as a good discriminator of outcomes [23] and there were clear stepwise increases in $\%FEV_1$ from 'lower quarter' to 'middle half' to 'upper quarter' in that age group. Further evidence regarding the robustness of the ranking process in identifying centres with better outcomes is provided in Appendix E.

Tables 3-5 summarise the IV use for the three groups of CF centres. When comparing among adults with the same lung disease severity; centres in the 'upper quarter' and 'middle half' used significantly more IV antibiotics, compared to centres in the 'lower quarter'. IV use was not statistically different between centres in the 'upper quarter' and 'middle half'. These results were consistent for both 2013 and 2014. These results were not explained by differences in case-mix between the three groups of CF centres (detailed analysis of case-mix factors in Appendix F), and similar results were obtained using regression modelling (see Appendix B).

Differences in the prescription of preventive therapies between the three groups of CF centres are summarised in Table 6. There was no clear signal in the prescription rates among the three groups and the differences were inconsistent from 2013-2014. It is unlikely these differences could explain the FEV_1 differences between the three groups since the direction of differences is somewhat paradoxical, with lowest prescriptions among centres in the 'middle half'. Higher prescription of preventive therapies should not improve FEV_1 of the 'upper quarter' (compared to the 'middle half' in 2013) whilst at the same time reduce FEV_1 of the 'lower quarter' (compared to the 'middle half' in 2014). Further analyses of preventive therapies data are presented in Appendix G.

4. DISCUSSION

This study found that UK adult CF centres with lowest FEV_1 are distinguished from centres with better FEV_1 by a lower use of IV antibiotics, rather than by prescription of preventive therapies. The ranking process used was robust in identifying the group of centres with better outcomes. Differences in case-mix did not explain the differences in IV use between centres. The 2013 results were consistent with 2014 results, suggesting that they are unlikely to be merely due to chance.

There are some differences between the results of this study and the ESCF results. Analysis of the ESCF 1995-1996 dataset showed similar IV days across all FEV_1 groups [2]. In the present study, those with FEV_1 <40% required much more IV while those with FEV_1 ≥70% were on very little IV, which would be consistent with preventive therapies being particularly effective at preventing exacerbations among those with higher FEV_1. Another ESCF analysis found that incidence of IV use has decreased from 1995 to 2005, but the decrease was partially offset by lower threshold among clinicians with respect to pulmonary symptoms and signs in initiating IV antibiotics [24]. In the present study, IV use remains high during the 2010's, especially among people with lower FEV_1. Survival among people with FEV_1 <30% has improved significantly over time [25], and it is not surprising this group would be particularly reliant on IV antibiotics. Analysis of the ESCF 1995-1996 dataset also found most pronounced differences in IV days but similar number of IV courses among adults. In this study, there were significant differences in both the number of IV courses and IV days between CF centres in the 'lower quarter' and other CF centres.

The results of this study echo the overall ESCF results from the 1990's and 2000's among North American centres. This is somewhat surprising, because the increasing availability and prescription of efficacious preventive therapies, including dry powder inhalers, have the potential to reduce the dependency on IV antibiotics. Indeed, nearly 90% of all adults in this study were prescribed at least one form of preventive therapy.

The limitations of a retrospective observational registry-based analysis have been previously discussed [26], but it is crucial to consider whether limitations of the UK CF registry dataset present a challenge to the validity of our findings. The UK CF registry do not routinely collect encounter-based data, hence potentially important information such as number of clinic visits are not available. In the 1995-1996 ESCF analyses, centres in upper quarter achieved more frequent clinic visits [2]. Data on preventive therapies are available within the UK CF registry, but are not accompanied by any adherence data. Previous studies have shown little relationship between preventive medications that are prescribed and preventive medications that are collected, with MPR of around 50% for preventive inhaled therapies [14]. Even when a prescription is collected, the amount of treatment taken can be highly variable [27]. Date- and time-stamped objective adherence measurement in adult suggests that median adherence is less than 36%, whilst self-reported adherence is 80% and clinicians' estimated adherence is poorly calibrated [15]. The data for IV antibiotics is very different is that it typically reflects treatment that was actually used. Hence the UK registry data would not reliably reflect how much of the prescribed preventive therapy is actually used. On the other hand, if the registry data suggest a preventive therapy is not

prescribed, it is likely the treatment has not been used. We could be relatively confident that adults not prescribed any preventive therapies were not using any of those therapies, hence they were different from those who were prescribed at least one type of preventive therapies. Comparing these two groups allows some sort of interpretation using the registry data for preventive therapy. The strong and consistent relationship that centres with lower FEV_1 have lower IV use contrasts with the inconsistent relationship with the metrics recording what preventive inhaled therapies were prescribed.

In using the ESCF methodology of aggregating centres into larger groups [2], we dealt with sample size issues and potential bias in annual review FEV_1 that makes differentiating quality of care between individual centres difficult. This allows us to confidently identify a group of centres with lower FEV_1 that also differed in a process of care measure. Age-for-age, there were clear stepwise differences in $\%FEV_1$ across the three different groups of centres that were not present during the transition age of 16 years (see Table 2 and Appendix E). These differences strongly suggest a genuine gradient of health outcomes from 'upper quarter' to 'lower quarter', which was not due to data or case-mix issues. Therefore, differences in the structure or processes of care, rather than case-mix, were likely to be responsible for the FEV_1 differences observed.

IV antibiotics are often taken as a surrogate for the frequency and severity of exacerbations. However, the 2003-2005 ESCF analyses show that centres using more IV did not have more exacerbations, but appeared to pay more attention to exacerbations and use more IV for the exacerbations that were paid attention to [8]. Similarly, our findings do not necessarily imply that centres with better FEV_1 were more prone to exacerbations, but simply that more exacerbations were treated. Data suggest that higher numbers of exacerbations are found when more attention is paid, e.g. with home-monitoring [28]. Thus, it is likely that many exacerbations are under-recognised and under-treated among people with CF. The 2003-2005 ESCF analyses also show that only around 50% of all exacerbations characterised by three / four Rabin criteria were actually treated with some form of additional antibiotics [8]. Those analyses, which stratified the distribution of IV use by indication, show that centres with highest FEV_1 treated more exacerbations and treated those exacerbations more aggressively (with IV rather than oral antibiotics) [8]. This could indicate that ESCF centres with the highest FEV_1 were able to monitor patients more attentively and intervene more often. The same metric of paying attention may well apply in the UK, with centres with better FEV_1 detecting and treating more exacerbations.

A recent ESCF analysis showed that treatment of exacerbations with antibiotics increases the likelihood of FEV_1 recovery following an acute decline [29]. Centres with low IV use may be under-recognising and under-treating exacerbations, leading to lower FEV_1. Given that high quality care is often associated with structures that allow teams to pay attention to the metrics that matter [5], these results may reflect care structures that are not adapted to pay sufficient attention in detecting exacerbations and emphasising prevention.

The continued dependence on IV use to achieve better FEV_1, in an era in which efficacious preventive therapies are increasing available and prescribed, should prompt the CF community to reflect on strategies for more effective utilisation of preventive therapies. Preventive inhaled therapies are specifically marketed around their ability to preserve lung health and to reduce the risk of exacerbations. In controlled clinical trials, with adherence rates of 80-100% [30], their efficacy is beyond doubt with 3-10% FEV_1 improvement and 20-50% risk reduction for exacerbations [6,7]. A likely reason for the failure of efficacious inhaled therapies to fully translate into clinical effectiveness is the real world adherence rates of only 35-50% [14,15]. There are on-going efforts to develop even more efficacious preventive therapies, but effective behaviour change interventions to support medication adherence is probably just as important for effective utilisation of preventive therapies.

5. CONCLUSIONS

In the 30 years since the benefit of intensive IV antibiotic use among people with CF was demonstrated, CF care continues to improve and therapeutic options, especially for preventive care, continue to increase. Yet the use of IV antibiotic treatment that is disruptive to people's life and associated with significant complications still distinguishes the adult centres in the UK with the lowest FEV_1 from centres with better FEV_1.

Intriguingly, centres with the best FEV_1 used similar amount of IV antibiotics as centres with moderate FEV_1 but seemed to have derived more benefit from their IV use. Analysis of the ESCF 1995-1996 dataset found that the centres with the highest FEV_1 appeared to pay more attention by reviewing people with CF more frequently and sending more respiratory samples [2]. It may be that the very best UK centres have developed relationships and structures that improve care by paying more attention to successful delivery of all care modalities, but this requires further investigation.

COMPETING INTERESTS

None declared.

FUNDING

This report is independent research arising from a Doctoral Research Fellowship, Zhe Hui Hoo, DRF-2014-07-092) supported by the National Institute for Health Research. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

CONTRIBUTORS

Each author had full access to the data and takes responsibility for the integrity and accuracy of the analysis. All authors contributed to and approved of the final submitted manuscript. HZH and MJW were responsible for study design, data analysis and interpretation, and the writing of the manuscript. MJC, SJW and REC contributed substantially to the data analysis and interpretation, and the writing of the manuscript.

ETHICS APPROVAL

NHS research ethics approval (Huntingdon Research Ethics Committee 07/Q0104/2) was granted for the UK CF Registry and each patient or legally authorised representative provided written informed consent for data collection and for use of anonymised data in research. Under the terms of the NHS ethics approval, the UK CF Trust steering committee approved the use of anonymised data in this study.

ACKNOWLEDGEMENTS

We would like to thank the UK CF Trust for supplying the data that made this analysis possible. We would also like to acknowledge all the people with CF in the UK who consent to be part of the UK CF registry.

REFERENCES

[1] Szaff M, Hoiby N, Flensborg EW. Frequent antibiotic therapy improves survival of cystic fibrosis patients with chronic Pseudomonas aeruginosa infection. Acta Paediatr Scand 1983;72:651–7.

[2] Johnson C, Butler SM, Konstan MW, Morgan W, Wohl ME. Factors influencing outcomes in cystic fibrosis: a center-based analysis. Chest 2003;123:20–7.

[3] Elborn JS, Prescott RJ, Stack BH, Goodchild MC, Bates J, Pantin C, et al. Elective versus symptomatic antibiotic treatment in cystic fibrosis patients with chronic Pseudomonas infection of the lungs. Thorax 2000;55:355–8.

[4] Konstan MW, VanDevanter DR, Rasouliyan L, Pasta DJ, Yegin A, Morgan WJ, et al. Trends in the use of routine therapies in cystic fibrosis: 1995-2005. Pediatr Pulmonol 2010;45:1167–72.

[5] Quinton HB, O'Connor GT. Current issues in quality improvement in cystic fibrosis. Clin Chest Med 2007;28:459–72.

[6] Ryan G, Singh M, Dwan K. Inhaled antibiotics for long-term therapy in cystic fibrosis. Cochrane Database Syst Rev 2011;3:CD001021.

[7] Yang C, Chilvers M, Montgomery M, Nolan SJ. Dornase alfa for cystic fibrosis. Cochrane Database Syst Rev 2016;4:CD001127.

[8] Schechter MS, Regelmann WE, Sawicki GS, Rasouliyan L, VanDevanter DR, Rosenfeld M, et al. Antibiotic treatment of signs and symptoms of pulmonary exacerbations: a comparison by care site. Pediatr Pulmonol 2015;50:431–40.

[9] Hoo ZH, Wildman MJ, Teare MD. Exploration of the impact of 'mild phenotypes' on median age at death in the U.K. CF registry. Respir Med 2014;108:716–21.

[10] Hurley MN, McKeever TM, Prayle AP, Fogarty AW, Smyth AR. Rate of improvement of CF life expectancy exceeds that of general population--observational death registration study. J Cyst Fibros 2014;13:410–5.

[11] Peckham D, Whitaker P. Drug induced complications; can we do more? J Cyst Fibros 2013;12:547–58.

[12] Southern KW. Acute renal failure in people with cystic fibrosis. Thorax 2007;62:472–3.

[13] Dasenbrook EC, Konstan MW, VanDevanter DR. Association between the introduction of a new cystic fibrosis inhaled antibiotic class and change in prevalence of patients receiving multiple inhaled antibiotic classes. J Cyst Fibros 2015;14:370–5.

[14] Quittner AL, Zhang J, Marynchenko M, Chopra PA, Signorovitch J, Yushkina Y, et al. Pulmonary medication adherence and health-care use in cystic fibrosis. Chest 2014;146:142–51.

[15] Daniels T, Goodacre L, Sutton C, Pollard K, Conway S, Peckham D. Accurate assessment of adherence: self-report and clinician report vs electronic monitoring of nebulizers. Chest 2011;140:425–32.

[16] Pego-Fernandes PM, Abrao FC, Fernandes FL, Caramori ML, Samano MN, Jatene FB. Spirometric assessment of lung transplant patients: one year follow-up. Clinics (Sao Paulo) 2009;64:519–25.

[17] Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011;365:1663–72.

[18] 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;127:725–34.

[19] Boelle PY, Viviani L, Busson PF, Olesen HV, Ravilly S, Stern M, et al. Reference percentiles for FEV(1) and BMI in European children and adults with cystic fibrosis. Orphanet J Rare Dis 2012;7:64.

[20] Hoo ZH, Daniels T, Wildman MJ, Teare MD, Bradley JM. Airway clearance techniques used by people with cystic fibrosis in the UK. Physiotherapy 2015;101:340–8.

[21] Doull I, Evans H; South and Mid Wales Paediatric Cystic Fibrosis Network. Full, shared and hybrid paediatric care for cystic fibrosis in South and Mid Wales. Arch Dis Child 2012;97:17–20.

[22] Nightingale JA, Osmond C. Does current reporting of lung function by the UK cystic fibrosis registry allow a fair comparison of adult centres? J Cyst Fibros 2017;16:585–91

[23] Schluchter MD, Konstan MW, Drumm ML, Yankaskas JR, Knowles MR. Classifying severity of cystic fibrosis lung disease using longitudinal pulmonary function data. Am J Respir Crit Care Med 2006;174:780–6.

[24] VanDevanter DR, Elkin EP, Pasta DJ, Morgan WJ, Konstan MW; Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Changing thresholds and incidence of antibiotic treatment of cystic fibrosis pulmonary exacerbations, 1995-2005. J Cyst Fibros 2013;12:332–7.

[25] George PM, Banya W, Pareek N, Bilton D, Cullinan P, Hodson ME, et al. Improved survival at low lung function in cystic fibrosis: cohort study from 1990 to 2007. BMJ 2011;342:d1008.

[26] Urschel S. Apples, oranges, and statistical magic: Limitations of registry studies and need for collaborative studies. J Heart Lung Transplant 2015;34:1136–8.

[27] Modi AC, Lim CS, Yu N, Geller D, Wagner MH, Quittner AL. A multi-method assessment of treatment adherence for children with cystic fibrosis. J Cyst Fibros 2006;5:177–85.

[28] Lechtzin N, Mayer-Hamblett N, West NE, Allgood S, Wilhelm E, Khan U, et al. Home Monitoring in CF to Identify and Treat Acute Pulmonary Exacerbations: eICE Study Results. Am J Respir Crit Care Med 2017 [Epub ahead of print]

[29] Morgan WJ, Wagener JS, Yegin A, Millar SJ, Konstan MW; Scientific Advisory Group, investigators; coordinators of the Epidemiologic Study of Cystic Fibrosis. Probability of treatment following acute decline in lung function in children with cystic fibrosis is related to baseline pulmonary function. J Pediatr 2013;163:115–7.

[30] Pugatsch T, Shoseyov D, Cohen-Cymberknoh M, Hayut B, Armoni S, Griese M, et al. Adherence pattern to study drugs in clinical trials by patients with cystic fibrosis. Pediatr Pulmonol 2016;51:143–6.

Table 1: Characteristics of adults with CF for the 3 groups of specialist CF centres ('upper quarter', 'middle half', 'lower quarter') for 2013-2014

Centre ranking	2013			2014		
	Upper quarter	Middle half	Lower quarter	Upper quarter	Middle half	Lower quarter
Number of centres	7	13	7	7	14	7
Number of adults with CF	1036	1952	1281	944	2255	1445
Age, mean (SD)	29.8 (10.9)	29.7 (10.2)	31.0 (10.5)	29.9 (10.8)	30.1 (10.6)	31.6 (10.6)
Female, (%)	467 (45.1)	903 (46.3)	566 (44.2)	436 (46.2)	1021 (45.3)	639 (44.2)
BMI, mean (SD)	22.9 (3.9)	22.6 (4.0)	22.3 (3.7)	22.8 (4.1)	22.7 (4.0)	22.3 (3.6)
Unadjusted % FEV_1, mean (SD)	68.1 (23.9)	65.2 (24.8)	62.1 (25.3)	69.4 (24.4)	66.8 (24.9)	62.1 (25.0)
Number of adults with FEV_1 and IV days data [§]	981	1867	1244	871	2167	1411
FEV_1 < 40%, (%)	135 (13.8)	343 (18.4)	294 (23.6)	125 (14.4)	359 (16.6)	331 (23.5)
FEV_1 40% to 69.9%, (%)	372 (37.9)	717 (38.4)	464 (37.3)	299 (34.3)	819 (37.8)	539 (38.2)
FEV_1 ≥ 70%, (%)	474 (48.3)	807 (43.2)	486 (39.1)	447 (51.3)	989 (45.6)	541 (38.3)
% Age-adjusted FEV_1, mean (SD)	104.5 (36.6)	100.3 (38.0)	96.0 (38.7)	105.4 (37.1)	101.1 (37.3)	95.0 (37.9)

[§] Missing data as detailed in Appendix B.

Table 2: % predicted FEV_1 at annual review for the three groups of specialist CF centres for 2013-2014, stratified according to age:

% predicted FEV_1 at annual review, median (IQR)	2013			2014		
	Upper quarter (n = 981)	Middle half (n = 1867)	Lower quarter (n = 1244)	Upper quarter (n = 871)	Middle half (n = 2167)	Lower quarter (n = 1411)
Age 16 – 19 years	82.1 (62.9 – 93.8)	75.9 (55.0 – 91.5)	72.6 (52.1 – 86.1)	80.4 (61.9 – 92.3)	80.0 (58.7 – 94.3)	71.6 (56.1 – 87.5)
Age 20 – 21 years	75.4 (50.5 – 91.4)	70.5 (48.0 – 88.4)	67.3 (46.8 – 86.7)	80.0 (59.5 – 93.1)	76.0 (57.5 – 91.7)	71.0 (43.0 – 87.1)
Age 22 – 23 years	69.2 (53.0 – 85.0)	66.7 (48.2 – 81.7)	69.4 (50.8 – 86.6)	75.1 (54.1 – 88.9)	67.0 (47.5 – 85.6)	65.9 (48.6 – 84.0)
Age 24 – 25 years	70.4 (52.8 – 85.7)	64.0 (45.9 – 84.5)	56.4 (35.1 – 83.0)	71.9 (58.1 – 84.6)	66.0 (46.9 – 85.0)	67.8 (47.8 – 79.0)
Age 26 – 27 years	62.5 (45.4 – 81.5)	63.2 (42.1 – 79.6)	61.8 (43.5 – 85.9)	60.3 (42.5 – 81.3)	59.0 (43.4 – 80.6)	63.5 (46.4 – 82.0)
Age 28 – 30 years	68.3 (46.2 – 85.3)	63.8 (46.7 – 83.0)	58.9 (40.0 – 80.1)	69.1 (54.2 – 86.0)	64.7 (45.6 – 80.1)	58.4 (39.3 – 81.5)
Age 31 – 33 years	65.3 (46.3 – 78.8)	58.0 (40.2 – 81.0)	54.2 (36.4 – 74.8)	62.5 (41.1 – 84.1)	62.5 (42.8 – 82.4)	55.7 (35.7 – 74.9)
Age 34 – 37 years	64.9 (47.1 – 84.5)	60.3 (46.4 – 76.2)	55.1 (39.1 – 76.8)	60.7 (44.0 – 81.6)	62.2 (47.6 – 80.7)	56.3 (39.1 – 78.0)
Age 38 – 44 years	66.3 (45.8 – 85.4)	63.6 (41.5 – 80.3)	59.7 (42.2 – 78.4)	74.4 (50.6 – 90.0)	61.6 (44.5 – 81.4)	56.8 (40.6 – 75.9)
Age ≥45 years	66.5 (40.9 – 85.8)	59.9 (45.0 – 82.5)	52.4 (35.9 – 76.6)	65.6 (48.8 – 91.6)	58.7 (41.9 – 81.2)	50.2 (35.0 – 72.9)

For 2013

P-value for upper quarter vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)

P-value for middle half vs lower quarter = 0.002 (after Bonferroni correction, p-value = **0.007**)

P-value for upper quarter vs middle half = 0.003 (after Bonferroni correction, p-value = **0.010**)

For 2014

P-value for upper quarter vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)

P-value for middle half vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)

P-value for upper quarter vs middle half = 0.002 (after Bonferroni correction, p-value = **0.007**)

*P-values were calculated for % predicted FEV_1 stratified according to age using the stratified Wilcoxon rank sum test (van Elteren test). This test is an extension of the Wilcoxon rank sum test that uses within-stratum ranks to compare two groups that are stratified. For references, see:

van Elteren PH. On the combination of independent two-sample tests of Wilcoxon. *Bull Int Stat Inst*1960;37(3):351-361.

Kawaguchi A, Koch GG. Sanon: an R package for stratified analysis with nonparametric covariable adjustment. *J Stat Softw*. 2015;67(9):1–37.

Table 3: Annual number of IV courses for the three groups of specialist CF centres ('upper quarter', 'middle half', 'lower quarter') for 2013 and 2014

	2013			2014		
	Upper quarter (n = 981)	Middle half (n = 1867)	Lower quarter (n = 1244)	Upper quarter (n = 871)	Middle half (n = 2167)	Lower quarter (n = 1411)
Annual number IV antibiotic courses, median (IQR)	1 (0 – 2)	1 (0 – 3)	1 (0 – 2)	1 (0 – 2)	1 (0 – 3)	1 (0 – 2)
Annual number IV antibiotic courses, stratified according to FEV_1, median (IQR)						
FEV_1 < 40%	3 (2 – 5)	3 (1 – 5)	2 (1 – 5)	3 (1 – 5)	3 (1 – 5)	2 (1 – 4)
FEV_1 40% to 69.9%	1 (0 – 3)	1 (0 – 3)	1 (0 – 2)	1 (0 – 3)	1 (0 – 3)	1 (0 – 2)
FEV_1 ≥ 70%	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)	0 (0 – 1)

For 2013

P-value for upper quarter vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)

P-value for middle half vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)

P-value for upper quarter vs middle half = 0.518 (after Bonferroni correction, p-value = 1)

For 2014

P-value for upper quarter vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)

P-value for middle half vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)

P-value for upper quarter vs middle half = 0.247 (after Bonferroni correction, p-value = 0.740)

*P-values were calculated for annual number of IV antibiotics courses stratified according to FEV_1 using the stratified Wilcoxon rank sum test (van Elteren test). This test is an extension of the Wilcoxon rank sum test that uses within-stratum ranks to compare two groups that are stratified. For references, see:

van Elteren PH. On the combination of independent two-sample tests of Wilcoxon. *Bull Int Stat Inst*1960;37(3):351-361.

Kawaguchi A, Koch GG. Sanon: an R package for stratified analysis with nonparametric covariable adjustment. *J Stat Softw*. 2015;67(9):1–37.

Table 4: Annual IV antibiotic days for the three groups of specialist CF centres ('upper quarter', 'middle half', 'lower quarter') for 2013 and 2014

	2013			2014		
	Upper quarter (n = 981)	Middle half (n = 1867)	Lower quarter (n = 1244)	Upper quarter (n = 871)	Middle half (n = 2167)	Lower quarter (n = 1411)
Annual IV antibiotic days, median (IQR)	14 (0 – 34)	14 (0 – 40)	10 (0 – 29)	13 (0 – 31)	14 (0 – 38)	12 (0 – 28)
Annual IV antibiotic days stratified according to FEV_1, median (IQR)						
FEV_1 < 40%	51 (28 – 79)	42 (14 – 77)	36 (14 – 78)	45 (20 – 80)	43 (17 – 73)	33 (14 – 70)
FEV_1 40% to 69.9%	15 (0 – 41)	15 (0 – 42)	14 (0 – 31)	14 (0 – 37)	17 (0 – 42)	14 (0 – 29)
FEV_1 ≥ 70%	0 (0 – 14)	0 (0 – 14)	0 (0 – 7)	0 (0 – 14)	0 (0 – 14)	0 (0 – 12)

For 2013

P-value for upper quarter vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)
P-value for middle half vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)
P-value for upper quarter vs middle half = 0.823 (after Bonferroni correction, p-value = 1)

For 2014

P-value for upper quarter vs lower quarter < 0.001 (after Bonferroni correction, p-value = **0.003**)
P-value for middle half vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)
P-value for upper quarter vs middle half = 0.299 (after Bonferroni correction, p-value = 0.898)

*P-values were calculated for annual IV antibiotic days stratified according to FEV_1 using the stratified Wilcoxon rank sum test (van Elteren test). This test is an extension of the Wilcoxon rank sum test that uses within-stratum ranks to compare two groups that are stratified. For references, see:

van Elteren PH. On the combination of independent two-sample tests of Wilcoxon. *Bull Int Stat Inst*1960;37(3):351-361.

Kawaguchi A, Koch GG. Sanon: an R package for stratified analysis with nonparametric covariable adjustment. *J Stat Softw*. 2015;67(9):1–37.

Table 5: Percentage of adults prescribed at least one IV antibiotics course in a year for 2013 and 2014

	2013			2014		
	Upper quarter (n = 981)	Middle half (n = 1867)	Lower quarter (n = 1244)	Upper quarter (n = 871)	Middle half (n = 2167)	Lower quarter (n = 1411)
People prescribed at least one course of IV antibiotics, (%)	552 (56.3)	1114 (59.7)	648 (52.1)	475 (54.5)	1243 (57.4)	780 (55.3)
People prescribed at least one course of IV antibiotics stratified according to FEV_1, (%)						
FEV_1 < 40%	124 (91.9)	287 (83.7)	237 (80.6)	112 (89.6)	305 (85.0)	266 (80.4)
FEV_1 40% to 69.9%	252 (67.7)	501 (69.9)	285 (61.4)	200 (66.9)	565 (69.0)	343 (63.6)
FEV_1 ≥ 70%	176 (37.1)	326 (40.4)	126 (25.9)	163 (36.5)	373 (37.7)	171 (31.6)

For 2013

P-value for upper quarter vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)

P-value for middle half vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)

P-value for upper quarter vs middle half = 0.573 (after Bonferroni correction, p-value = 1)

For 2014

P-value for upper quarter vs lower quarter = 0.014 (after Bonferroni correction, p-value = **0.041**)

P-value for middle half vs lower quarter = 0.001 (after Bonferroni correction, p-value = **0.002**)

P-value for upper quarter vs middle half = 0.750 (after Bonferroni correction, p-value = 1)

*P-values were calculated for the percentage of adults prescribed at least one IV antibiotics course in a year stratified according to FEV_1 using the Cochran-Mantel-Haenszel test. This test is an extension of the chi-square test, and is used to determine the presence of consistent difference in proportions across stratified subgroups. For references, see:

Cochran WG. Some Methods for Strengthening the Common χ2 Tests. *Biometrics* 1954;10(4):417-351.

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22(4):719-748.

Table 6: Prescription of preventive therapies for the three groups of specialist CF centres ('upper quarter', 'middle half', 'lower quarter') for 2013 and 2014

	2013			2014		
	Upper quarter (n = 983)	Middle half (n = 1869)	Lower quarter (n = 1244)	Upper quarter (n = 871)	Middle half (n = 2167)	Lower quarter (n = 1411)
People prescribed any form of preventive therapy, (%)	873 (88.8)	1621 (86.7)	1079 (86.7)	772 (88.6)	1888 (87.1)	1300 (92.1)
People prescribed any form of preventive therapy stratified according to FEV_1, (%)						
FEV_1 < 40%	135 (100.0)	335 (97.7)	281 (95.6)	124 (99.2)	349 (97.2)	330 (99.7)
FEV_1 40% to 69.9%	354 (95.2)	661 (92.2)	435 (93.8)	291 (97.3)	774 (94.5)	525 (97.4)
FEV_1 ≥ 70%	384 (80.7)	625 (77.3)	363 (74.7)	357 (79.9)	765 (77.4)	445 (82.3)

For 2013

P-value for upper quarter vs lower quarter = 0.005 (after Bonferroni correction, p-value = **0.015**)

P-value for middle half vs lower quarter = 0.485 (after Bonferroni correction, p-value = 1)

P-value for upper quarter vs middle half = 0.019 (after Bonferroni correction, p-value = 0.057)

For 2014

P-value for upper quarter vs lower quarter = 0.363 (after Bonferroni correction, p-value = 1)

P-value for middle half vs lower quarter < 0.001 (after Bonferroni correction, p-value **< 0.001**)

P-value for upper quarter vs middle half = 0.058 (after Bonferroni correction, p-value = 0.173)

*P-values were calculated for the prescription of any pulmonary preventive therapies (inhaled antibiotics / inhaled mucolytics / long-term oral macrolide) stratified according to FEV_1 using the Cochran-Mantel-Haenszel test. This test is an extension of the chi-square test, and is used to determine the presence of consistent difference in proportions across stratified subgroups. For references, see:

Cochran WG. Some Methods for Strengthening the Common χ2 Tests. *Biometrics* 1954;10(4):417-351.

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22(4):719-748.