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Title: Real-world adherence among adults with cystic fibrosis is low – a retrospective analysis of the CFHealthHub digital learning health system

Short title: Real-world adherence in CF is low

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PARI Pharma GmbH provided funding to the technical team at the University of Manchester, where Pauline Whelan and John Ainsworth are based, to create a medication reporting component within the CFHealthHub software which is separate to the work reported here. No conflict exists for Zhe Hui Hoo, Nikki Totton, Simon Waterhouse, Jen Lewis, Carla Girling, Michael Bradburn, Madelynne Arden, Sophie Dawson, Sarah Millward, Kate Barnett, Jane Dewar, Helen Barr, Gauri Saini, Elizabeth Shepherd, Mary Carroll, Mark Allenby, Thomas Daniels, Julia Nightingale, Michelle Lowther, Charlotte Carolan, Charlotte Clarke, Rachel Szczepanski, Marlene Hutchings, Frank Edenborough, Rachael Curley and Martin Wildman.

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Abbreviations list

CF – cystic fibrosis

CFTR – cystic fibrosis transmembrane conductance regulator

LHS – learning health system

NICE – National Institute for Health and Care Excellence

UK – United Kingdom

Inhaled antibiotics and mucolytics can prevent exacerbations and maintain lung function in cystic fibrosis (CF). However, treatment adherence is usually low[1-3] (even for CFTR modulators[4]) which undermines treatment effectiveness.[2] Single-center studies[1] or studies lacking objective adherence data[2] complicate the accurate representation of CF adherence levels. In addition, adherence may be over-estimated by convenience sampling and adherence definitions not accounting for minimum required treatment.[3]

The National Institute for Health and Care Excellence (NICE) has recently published UK CF quality indicators recommending that center-level adherence data are presented,[5] providing an impetus to explore how to fairly represent center-level adherence. We therefore analyzed objective nebulizer adherence data available in the CFHealthHub digital Learning Health System (LHS, ISRCTN14464661) between November 2015 and May 2019 to understand adherence among adults with CF. A secondary aim was to replicate our earlier study, which suggested that calculations based on agreed rather than normative regimens can over-estimate adherence.[3]

METHODS

This retrospective multi-center observational study included adult CF centers in Sheffield (n=95), Southampton (n=101) and Nottingham (n=103), which are first-wave CFHealthHub digital LHS centers. Participants aged ≥16y were diagnosed by standard criteria[6] and used data-logging nebulizers (eTrack®, PARI Pharma GmBH and Bi-neb®, Philips Healthcare) for ≥56 days. Participants were aware that their nebulizer would record every dose of medication taken, and date- and time-stamped adherence data would be transferred in real-time to the CFHealthHub digital platform but adherence data were inaccessible during the study period. Lung transplant recipients were excluded. Researchers at each site extracted inhaled therapy prescriptions and demographic data (age, gender, pancreatic status, *Pseudomonas aeruginosa* status as defined by clinicians,[7] body mass index, $\%FEV_1$, intravenous antibiotics use) from clinical records. Adherence was measured over a 56-day post-recruitment period whilst clinicians and participants were blinded to the data, and calculated as a mean of all daily adherence values.

'Unadjusted adherence' was calculated as the percentage of total nebulizers completed against prescribed doses agreed between adults with CF and clinicians, i.e. the denominator was personalized rather than standardized.[3] 'Normative adherence' involved standardized numerator adjustment (daily maximum completed doses capped at 100%) and standardized denominator adjustment based on clinical characteristics (ensuring those without chronic *Pseudomonas aeruginosa* were on at least a daily mucolytic dose and those with chronic *Pseudomonas aeruginosa* were on at least once daily mucolytic plus twice daily antibiotic doses) to reflect effectiveness of treatment regimens.[3] To calculate normative adherence, people with chronic *Pseudomonas aeruginosa* prescribed only twice daily inhaled antibiotics or once daily dornase alfa would have their

data analyzed using a daily denominator of "3" since consensus guidelines recommend both mucolytic and antibiotic for this subgroup.[8] There is no denominator adjustment if the minimum required doses were already fulfilled (i.e. the prescribed doses define the denominator), for example a person on twice daily tobramycin, daily dornase alfa and twice daily hypertonic saline. In this example, the normative adherence is 60% (3/5) if tobramycin and dornase alfa were used but not hypertonic saline.

Analyses were performed using R v3.6.1 (www.r-project.org). Descriptive statistics (median and IQR) were generated, including results for the chronic *Pseudomonas aeruginosa* sub-group. The agreement between unadjusted adherence and normative adherence were assessed with 'difference-versus-average' plots. The median difference and 95% confidence interval[9] were calculated to assess whether there was a systematic difference between the two, as well as Wilcoxon signed-rank test with $p<0.05$ considered statistically significant. The sample size is pragmatic with all available data used.

RESULTS

This study included 318 adults with 146 (46%) females and 166 (52%) have chronic *Pseudomonas aeruginosa*. Adults with concurrent use of dry powder inhaler(s) have slightly lower adherence (Table 1). Among adults only on nebulized treatment(s), unadjusted adherence was 41.5% (IQR 15.1-74.1%) whilst normative adherence was 31.6% (IQR 10.5-60.9%); median paired difference 9.6% (95% CI 7.4-11.8%), p-value <0.0001. The differences between unadjusted vs normative adherence were particularly pronounced in the chronic *Pseudomonas aeruginosa* sub-group, where the figures were 38.9% (IQR 19.8-71.4%) and 26.0% (IQR 10.8-49.2%) respectively; median paired difference 14.5% (95% CI 11.2-19.7%), p-value <0.0001 (Figure 1). The cohort-level median adherence was unaffected by the inclusion of dry powder inhalers or alternative definition of *Pseudomonas aeruginosa* status, further results are available by contacting the corresponding author.

DISCUSSION

In the largest and first multi-center study using standardized measurement conventions and objective data capture among adults with CF, we confirmed low real-world nebulizer adherence. Half of adults had objective adherence <1/3, despite a universal healthcare system that provides nebulized medications free at the point-of-care. We replicated our earlier finding that calculation based on agreed regimens generates higher center-level adherence compared to calculations based on regimens defined by consensus around effectiveness (41.5% vs 31.6%). Not everyone is prescribed treatments defined by effectiveness since regimens may be modified with the hope of reducing burden, which creates the discrepancy between unadjusted and normative adherence. This

discrepancy is most obvious among those with chronic *Pseudomonas aeruginosa* where the minimum denominator for normative adherence (population standardization based on consensus around effectiveness) is three doses/day. Prescription of inhaled therapies differs between UK specialist centers despite guidance by the CF Trust Standards of Care,[6] for example center-level dornase alfa prescription varied between 46.6% and 87.4%.[10] The median paired difference between unadjusted vs normative adherence in this study was larger than our earlier study (9.6% vs 2.6-5.1%), probably due to high rates of inhaled antibiotic prescribed in Sheffield.[3]

Limitations include selective recruitment since not all adults at the participating centers were included and adherence was only measured over the initial 56 days post-recruitment. People with lowest adherence are probably the most difficult to reach[3] and long-term adherence also declines over time;[4] hence adherence levels are still likely to be over-estimated. Data on CFTR modulators use were unavailable, but only ~5% of adults were eligible during the study period so impact of modulator use is expected to be small.

In conclusion, our study shows low medication adherence among adults with CF. Calculating adherence levels without considering sampling strategies and the clinical appropriateness of treatment prescription may over-estimate effective adherence, highlighting the impact of data issues on center-level adherence.

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Guarantor statement:
MJW is the guarantor of the content of the manuscript.

Author contribution:
HZH, MJW: concept and design. SD, ES, ML, CC, CC: data acquisition. NT, SW, JL, MB: data analysis. HZH: drafting the manuscript. All authors involved in the interpretation of data; and critically revised the manuscript and approved the final draft.

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Role of the sponsors
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Ethics approval:

Regulatory approval for this study was obtained from London-Brent NHS Research Ethics Committee (reference number: 17/LO/0032).

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Table 1: Demographics and adherence levels of adults only on nebulized treatment(s) vs adults with concurrent use of dry powder inhaler(s)

	Only nebulized treatment(s) † (*n* = 299)	Concurrent use of dry powder inhaler(s) ‡ (*n* = 19)
Age in years, median (IQR)	26 (20 to 34)	28 (25 to 35)
Female, *n* (%)	137 (46%)	9 (47%)
Pancreatic insufficient, *n* (%)	198 (84%)	13 (87%)
Chronic *Pseudomonas aeruginosa* infection, *n* (%)		
Based on clinicians' judgement Ω	147 (49%)	19 (100%)
Based on the Leeds criteria Δ	124 (42%)	16 (84%)
Body mass index, median (IQR)	22.0 (20.2 to 24.6)	21.6 (19.6 to 27.0)
%FEV_1, median (IQR)	73.0 (52.4 to 87.5)	74.9 (57.6 to 86.8)
IV antibiotic days, median (IQR)	14 (0 to 28)	14 (12 to 14)
Number of daily prescribed nebulizer dose(s), *n* (%)		
1	102 (34%)	11 (58%)
2	50 (17%)	3 (16%)
3	86 (29%)	4 (21%)
4	35 (12%)	0
5	17 (6%)	0
6+	9 (3%)	1 (5%)
Prescription type, *n* (%)		
Mucolytic only	126 (42%)	13 (68%)
Antibiotic only	22 (7%)	0
Both mucolytic and antibiotic	148 (49%)	6 (32%)
Adult CF centers, *n* (%)		
Sheffield	95 (32%)	3 (16%) ϕ
Southampton	101 (34%)	8 (42%) ϕ
Nottingham	103 (34%)	8 (42%) ϕ
% Unadjusted adherence α, median (IQR)	41.5 (15.1 to 74.1)	18.7 (7.2 to 65.8)
% Normative adherence β, median (IQR)		
P. aeruginosa status according to clinicians' judgement	31.6 (10.5 to 60.9)	18.7 (6.9 to 53.4)
P. aeruginosa status according to the Leeds criteria	32.2 (11.1 to 62.1)	15.8 (3.0 to 31.0)

† There was no missing adherence data for all adults only on nebulized treatment(s). There were missing data for age (n=24, 8%), pancreatic status (n=64, 21%), body mass index (n=28, 9%), %FEV_1 (n=35, 12%) and IV days (n=27, 9%).

‡ There was no missing adherence data for all adults using dry powder inhaler(s). There were missing data only for pancreatic status (n=4, 21%).

Ω This is the number of participants defined as being chronically infected with *P. aeruginosa* according to clinicians' judgement.[7] Among the adults included in the studies, Pseudomonas status was unavailable for 18 (6%) adults and these adults were deemed to be not chronically infected with *P. aeruginosa*.

Δ This is the number of participants defined as being chronically infected with *P. aeruginosa* according to the Leeds criteria.

ϕ The percentage reported here reflects how the 19 dry powder inhaler users are distributed among the three adult CF centers – the majority of CFHealthHub participants using dry powder inhaler(s) received care at Southampton Adult CF Centre or Wolfson Adult CF Centre. However, the percentage should not be used to infer that that dry powder inhaler use is lower in Sheffield Adult CF Centre compared to Southampton Adult CF Centre or Nottingham Adult CF Centre. Very few of the CFHealthHub participants have dry powder inhaler(s) in their inhaled treatment regimen, a substantial proportion of adults in each center have yet to be recruited as of May 2019 and the proportion of recruited adults also differed among the three centers. It is possible that many of the non-recruited adults have dry powder inhaler(s) in their inhaled treatment regimen. As such, the proportion of dry powder inhaler(s) users of each center should only be compared when the majority of adults in each center have been recruited into CFHealthHub.

α For adults with concurrent use of dry powder inhaler(s), only adherence via data-logging nebulizers can be objectively measured. Therefore, adherence levels were calculated only for nebulizer use. For example, the adherence level for someone on dornase alfa once daily and tobramycin dry powder inhaler twice daily will be calculated for dornase alfa use only. If that person had adherence of 70% to dornase alfa, then 70% was taken as his / her global adherence to inhaled therapies.

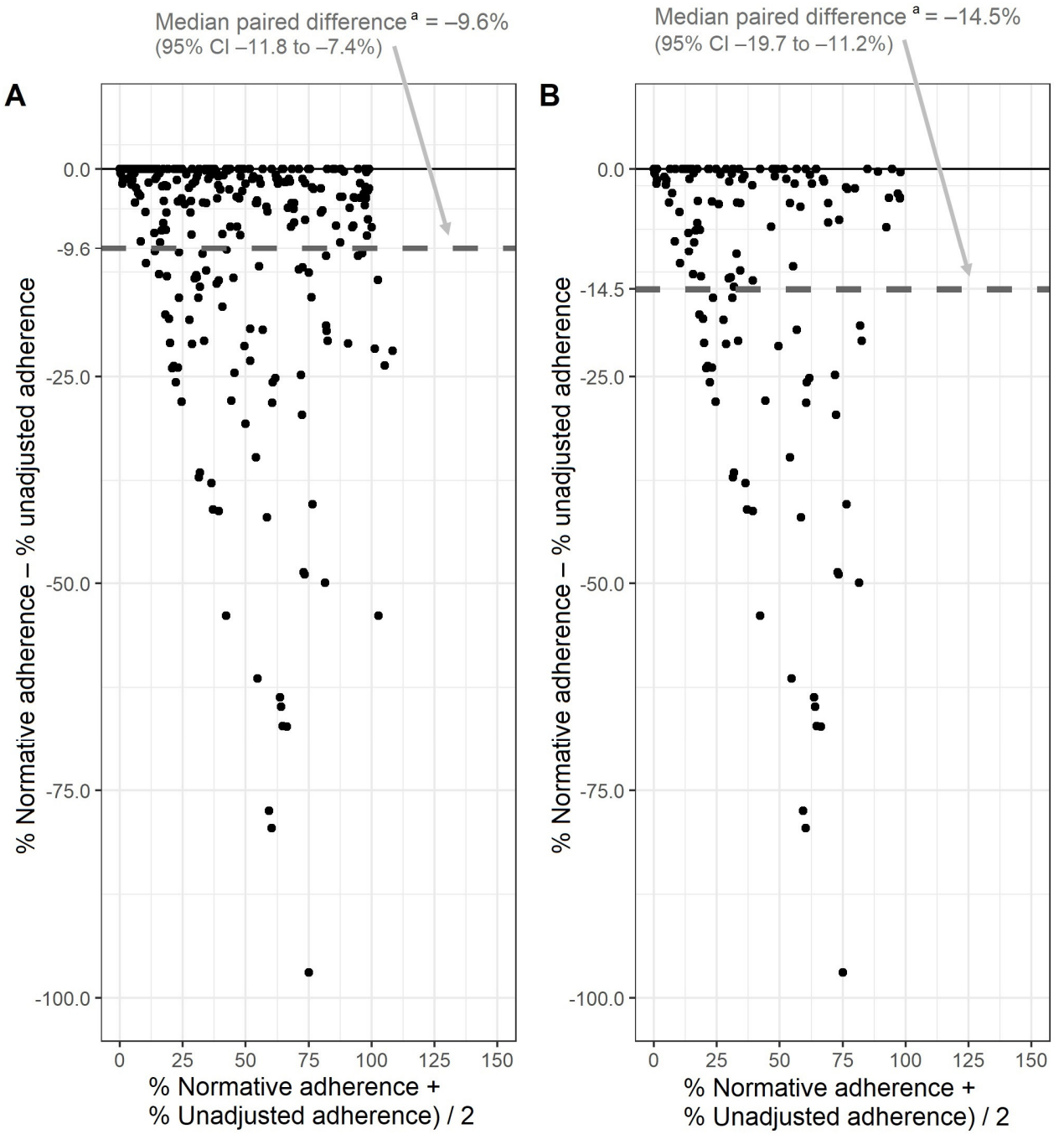
β To calculate normative adherence, denominator adjustment would only be carried out among adults who did not fulfil the minimum required doses (i.e. a minimum of once daily mucolytic for adults without chronic *P. aeruginosa* infection; a minimum of once daily mucolytic and twice daily antibiotics for adults with chronic *P. aeruginosa* infection). For adults with concurrent use of dry powder inhaler(s), the use of dry powder inhaler would be taken into account for the denominator adjustment to calculate normative adherence. For example, in a study subject with chronic *P. aeruginosa* infection prescribed with a nebulized mucolytic and twice daily dry powder inhaled antibiotics, no extra nebulizer doses will be added to the denominator.

FIGURE LEGENDS

[a] The non-parametric method [9] used to estimate the center-level paired difference between two methods to calculate adherence level involves first calculating all n differences d_1, d_2 … d_n. We then calculate all possible n(n+1)/2 averages of pairs of the differences $(d_1 + d_2)/2$, $(d_1 + d_3)/2$ etc. including $(d_1 + d_i)/2$ for i = 1, 2, … n, and then selecting the median of the averages. This method can also be used to find confidence intervals for this median.[9]

[b] Around 10-15% of the unadjusted adherence values were similar to normative adherence, especially among those with low adherence levels. However, unadjusted adherence values over-estimated adherence levels by >5% in the vast majority of the participants with a center-level median paired difference of 9.6% (95% CI 7.4-11.8%). Among those with nebulizer over-use (unadjusted adherence >100%), the difference between unadjusted and normative adherence could be up to 40-100%.

Figure 1 [b]: 'Difference vs average' plots for % normative adherence and % unadjusted adherence for all adults only on nebulized treatment(s) (A) and the subset with chronic *P. aeruginosa* infection (B)



[a] The non-parametric method [9] used to estimate the center-level paired difference between two methods to calculate adherence level involves first calculating all n differences d_1, d_2 … d_n. We then calculate all possible $n(n+1)/2$ averages of pairs of the differences $(d_1 + d_2)/2$, $(d_1 + d_3)/2$ etc. including $(d_1 + d_i)/2$ for i = 1, 2, … n, and then selecting the median of the averages. This method can also be used to find confidence intervals for this median.[9]

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