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FULL TITLE: Intravenous antibiotic use and exacerbation events in an adult cystic fibrosis centre: a prospective observational study

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ABSTRACT:

Introduction

In CF, people with higher FEV_1 are less aggressively treated with intravenous (IV) antibiotics, with resultant negative impact on their health outcomes. This could be entirely clinician-driven, but patient choice may also influence IV use. In this prospective observational study, we explored IV recommendations by clinicians and IV acceptance by adults with CF to understand how clinical presentations consistent with exacerbations resulted in IV use.

Methods

Clinical presentations consistent with exacerbations, IV recommendation by clinicians and IV acceptance by patients were prospectively identified for every adult with CF in Sheffield throughout 2016, excluding those who had lung transplantation (*n*=7) or on ivacaftor (*n*=13). Relevant demographic data, e.g. $\%FEV_1$, were extracted from medical records. Multi-level mixed-effects logistic regression models were used to compare IV recommendations vs non-recommendations for all clinical encounters, and IV acceptance vs non-acceptance for all IV recommendations.

Results

Among 186 adults (median age 27 years, median FEV_1 78.5%), there were 434 exacerbation events and 318 IV use episodes following 1010 clinical encounters. Only 254 (58.5%) of exacerbations were IV treated. A diagnosis of exacerbation, higher number of symptoms and lower $\%FEV_1$ were independent predictors for IV recommendation by clinicians. Higher number of symptoms and lower $\%FEV_1$ were also independent predictors for IV acceptance by adults with CF.

Conclusions

Lower IV use among adults with higher $\%FEV_1$ was influenced by both clinicians' and patients' decisions. Using IV antibiotics as an exacerbation surrogate could under-estimate exacerbation rates and conceal differential treatment decisions according to varying clinical characteristics.

KEYWORDS: Cystic fibrosis; epidemiology; patient outcome assessment; pulmonary exacerbation

1. INTRODUCTION

In CF, "pulmonary exacerbations" are episodic acute events causing lung damage, usually precipitated by infection and manifest as acute worsening of symptoms and/or drop in lung function (FEV_1) [1, 2]. Exacerbations are associated with excess mortality, accelerated FEV_1 decline, lower quality of life and higher healthcare costs [3]. They may also be the primary driver of progressive lung disease in CF [4]. There is no consensus regarding the definition and diagnosis of exacerbations [1], though on-going innovative studies such as STOP2 attempt to identify the best exacerbation treatment practices [5]. Not surprisingly, there are currently differing thresholds to initiate treatment and variations in treatment choices [6-11]. Prompt and aggressive treatments of exacerbations are nonetheless important – initiating additional antibiotics is associated with FEV_1 recovery [12] and intravenous (IV) antibiotics tend to give the best outcomes [13].

The Epidemiologic Study of CF (ESCF) showed that children with higher FEV_1 were less aggressively treated with IV antibiotics when presenting with acute FEV_1 decline which may indicate an exacerbation [14]. A similar study has not been done among adults. Also, it remains unclear as to what extent IV treatment is influenced by the decisions of children with CF, their parents or clinical teams. People with CF may refuse treatment [15, 16] and perceive exacerbations differently from clinicians [17]. Indeed, multiple steps are needed before IV treatment is initiated (see Figure 1) and each link in this chain is susceptible to variation.

We aim to prospectively sample the links in the exacerbation-treatment chain and to understand the relationship between exacerbations, symptoms, other clinical characteristics and IV treatments among adults with CF. We therefore set out to determine the factors that influenced IV recommendation by clinicians during clinical encounters and IV acceptance by adults with CF. We also quantified the frequency of presentations consistent with exacerbations in our centre throughout 2016 and compared the rates of exacerbation events against IV treatments.

2. MATERIAL AND METHODS

This single-centre prospective observational study included all adults with CF in Sheffield diagnosed according to the UK CF Trust criteria [18], excluding those who had lung transplantation (n=7) or on ivacaftor (n=13). These adults were excluded because both treatments have transformative effects on lung health, such that exacerbation rates no longer represent that of a typical adult with CF [19, 20]. Regulatory approval for this study was obtained from NHS Health Research Authority (IRAS number 210313).

Exacerbation data were prospectively collected between 1st January and 31st December 2016. During every encounter involving clinician review, exacerbations were diagnosed on clinical grounds by experienced CF physicians. The presence of Fuchs' features [21], clinicians' recommendation for

IV treatment and patients' acceptance of IV treatment were also recorded during every clinical encounter. Demographic (age, gender, genotype, pancreatic status, CF related diabetes, *Pseudomonas aeruginosa* status) and clinical (body mass index, FEV_1 and IV antibiotics episodes) data were collected by two investigators (HZH and RC / HZH and NRB) independently reviewing paper notes and electronic records. Where data from two investigators differed, both investigators re-reviewed the original data and arrived at a consensus to ensure data accuracy [22].

Sequential IV use separated by <7 days was combined and counted as a single episode [23]. Negative binomial regression was used to analyse exacerbation and IV use events, since these are count data with over-dispersion (~40% of the population have no IV use over a 1-year period [24]). Previous studies have demonstrated the suitability of negative binomial regression in handling this type of data [25] and it was also used in recent landmark CF-related clinical trials [20, 26]. $\%FEV_1$ was calculated using Global Lung Function Initiative equations [27]. Best $\%FEV_1$ (highest reading in the calendar year of 2016 for each participant) was used for analysis since it is most reflective of the true baseline $\%FEV_1$ [14].

Cohort characteristics and clinical parameters during clinical encounters were described. Factors associated with IV treatments were explored using mixed-effects modelling (random effect at individual level) to account for within-subject serial correlation because participants had >1 clinical encounter during 2016. Binary logistic regression was used to compare clinical encounters in which clinicians recommended IV vs IV not recommended. Among all encounters in which IV treatment were recommended, IV acceptance by adults with CF vs IV not accepted were similarly compared.

The multi-level mixed-effects binary logistic regression models were fitted with clinicians' diagnosis of exacerbation, number of Fuchs' features, season of clinical encounter, $\%FEV_1$ categories, pancreatic status, *P. aeruginosa* status and gender as fixed effect. Presence of exacerbation and number of Fuchs' features (as a proxy for the severity of exacerbation symptoms) would be expected to influence treatment decisions. Other covariates were chosen based on previous studies. IV treatments were more common during winter months [28]. People with higher FEV_1 were less aggressively treated with IV antibiotics [14]. IV use was consistently associated with pancreatic status, *P. aeruginosa* status, gender and $\%FEV_1$ in recent UK registry analysis.[24] $\%FEV_1$ were categorised as <40%, 40-69.9% and ≥70%, since these are internationally accepted to reflect different states of lung health [29] and are also applicable to UK data [24].

SPSS v25 (IBM Corp) was used for analyses. P-value <0.05 was considered statistically significant. A complete case approach was used for analyses since the only missing data was FEV_1 in one participant. The sample size of this study was pragmatic. There were >10 events per covariate included in both logistic regression models, which should represent adequate power [30].

2.1 Sensitivity, subgroup and further analyses

Clinical encounters among the participants can be broadly divided into reviews whereby IV treatments were pre-agreed prior to face-to-face encounters (e.g. direct hospital admissions) and reviews whereby treatment decisions were made following face-to-face encounters (e.g. routine clinics). All clinical encounters were included in the main analyses since regardless of the presentation route, ultimately clinicians would still have to offer treatments that were accepted by participants for the initiation of any IV treatments. To understand potential bias from pre-agreed treatments, a sensitivity analysis of IV recommendations and acceptance excluding data for direct hospital admissions was reported in Appendix B. Irrespective of indication (e.g. to treat exacerbation or 'elective IV' [31]), all IV recommendations were included in the main analyses for a comprehensive understanding of IV use epidemiology. Appendix C specifically explored IV treatment of exacerbations, including looking at relevant presenting features [14, 32]. In light of the findings from our analyses, Appendix D compared exacerbation and IV use frequencies against $\%FEV_1$ to highlight their discrepancies. Appendix E reported a subgroup analysis involving adults with objective nebuliser adherence data to explore the potential association between adherence and IV acceptance.

3. RESULTS

This study included 186 adults (90, 48.4% were females), with median age 27 years (IQR 21-34 years) and median $\%FEV_1$ 78.5% (IQR 58.5-89.6%); see Table 1. Among them, 63 (33.9%) did not receive IV antibiotics in 2016 but only 36 (19.4%) had no detectable exacerbations. The mean number of IV courses/adult/year was 1.7 (95% CI 1.4-2.0), whilst the mean number of exacerbations/adult/year was 2.3 (95% CI 2.0-2.8).

Figure 2 shows the incomplete overlap between exacerbation and IV use. Figure 3 summarises the clinical parameters during clinical encounters. Following 1010 clinical encounters, 434 exacerbation events were detected and 318 IV courses were initiated. Of those IV courses, 64 (20.1%) were not for exacerbations. IV antibiotics were also used prophylactically (e.g. pre-surgery), to control chronic infection/inflammation or for eradication (e.g. *M. abscessus*). IV were actually recommended on 388 occasions but declined by participants on 74 occasions (19.1%). Only 254 (58.5%) of detected exacerbations were IV treated.

Table 1: Demographic and clinical characteristics of the study subjects

Excluded	
Lung transplantation, *n*	7
On ivacaftor, *n*	13
Included, *n*	**186**
Age in years, median (IQR)	27 (21 to 34)
Female, *n* (%)	90 (48.4)
Genotype status:¶	
≥1 unknown mutation(s), *n* (%)	15 (8.1)
≥1 class IV-V mutation(s), *n* (%)	34 (18.3)
Homozygous class I-III, *n* (%)	137 (73.7)
Pancreatic insufficient,† *n* (%)	145 (78.0)
CF related diabetes,‡ *n* (%)	54 (29.0)
P. aeruginosa status:§	
No *P. aeruginosa*, *n* (%)	78 (41.9)
Intermittent *P. aeruginosa*, *n* (%)	29 (15.6)
Chronic *P. aeruginosa*, *n* (%)	79 (42.5)
BMI, median (IQR)	23.2 (20.4 to 26.0)
Best %FEV_1,Ω median (IQR)	78.5 (58.5 to 89.6)
IV days	
Mean (95% CI)ϕ	26.2 (22.4 to 30.0)
Median (IQR)	14 (0 to 40)
IV use episodes	
0, *n* (%)	63 (33.9)
1, *n* (%)	48 (25.8)
2, *n* (%)	27 (14.5)
3, *n* (%)	16 (8.6)
4, *n* (%)	9 (4.8)
≥5, *n* (%)	23 (12.4)
Mean (95% CI)ϕ	1.7 (1.4 to 2.0)
Median (IQR)	1 (0 to 3)
Exacerbation events	
0, *n* (%)	36 (19.4)
1, *n* (%)	43 (23.1)
2, *n* (%)	37 (19.9)
3, *n* (%)	25 (13.4)
4, *n* (%)	14 (7.5)
≥5, *n* (%)	31 (16.7)
Mean (95% CI)ϕ	2.3 (2.0 to 2.8)
Median (IQR)	2 (1 to 3)

¶ Genotype status was defined according to international consensus [33]. Homozygous class I-III mutations indicate 'severe genotype'.

† Pancreatic insufficiency was diagnosed by the clinical team on the basis of ≥2 faecal pancreatic elastase levels <200μg/g stool and symptoms consistent with maldigestion and malabsorption, in accordance to the UK Cystic Fibrosis (CF) Trust guideline.

‡ CF related diabetes was diagnosed by the clinical team on the basis of oral glucose tolerance test and continuous subcutaneous glucose monitoring results, in accordance to the UK CF Trust guideline.

§ *P. aeruginosa* status was determined according to the Leeds criteria [34].

Ω One of the study subjects did not provide any %FEV_1 readings due to the inability to perform spirometry.

ϕ The mean and 95% confidence intervals are calculated using a negative binomial regression model.

Table 2: Summary of results from the multi-level mixed-effects binary logistic regression models (random effect at individual level, to account for repeated measures within an individual) for IV recommendation by clinicians and for IV acceptance by adults with CF

Predictors	Comparing IV recommended vs IV not recommended by clinicians among all 1010 clinical encounters (in 186 adults)[Ψ]		Comparing IV accepted vs IV not accepted by adults with CF among all 388 recommended courses of IV (in 128 adults)[ϕ]	
	Adjusted odds ratio[†] (95% CI)	P-value	Adjusted odds ratio[‡] (95% CI)	P-value
Diagnosed as exacerbation[¶] by clinicians	**8.46 (5.59 to 12.79)**	**< 0.001**	1.08 (0.49 to 2.39)	0.856
Fuchs' score ≥4	**3.85 (2.40 to 6.17)**	**< 0.001**	**2.64 (1.30 to 5.35)**	**0.007**
Season of clinical encounter (Winter as reference)		**< 0.001**		**< 0.001**
Autumn – Sep, Oct, Nov	**0.32 (0.20 to 0.51)**	**< 0.001**	**0.24 (0.10 to 0.55)**	**0.001**
Summer – Jun, Jul, Aug	**0.38 (0.23 to 0.62)**	**< 0.001**	**0.12 (0.05 to 0.27)**	**< 0.001**
Spring – Mar, Apr, May	**0.29 (0.18 to 0.48)**	**< 0.001**	**0.17 (0.07 to 0.41)**	**< 0.001**
FEV_1 categories (≥70% as reference)		**0.021**		**0.002**
40 – 69.9%	**1.80 (1.12 to 2.79)**	**0.009**	**2.48 (1.20 to 5.12)**	**0.014**
<40%	1.71 (0.90 to 3.25)	0.100	**7.86 (2.03 to 30.40)**	**0.003**
Pancreatic insufficient	**5.75 (2.87 to 11.50)**	**< 0.001**	0.33 (0.04 to 2.98)	0.323
P. aeruginosa status [§] (no *P. aeruginosa* as reference)		**< 0.001**		0.176
Intermittent *P. aeruginosa* infection	**2.76 (1.48 to 5.13)**	**0.001**	1.48 (0.45 to 4.89)	0.523
Chronic *P. aeruginosa* infection	**2.48 (1.52 to 4.04)**	**< 0.001**	0.61 (0.25 to 1.48)	0.278
Female	1.17 (0.78 to 1.76)	0.454	1.04 (0.53 to 2.06)	0.906

[Ψ] For this model: Akaike Corrected Information Criterion (AIC) = 5213.2; Bayesian Information Criterion (BIC) = 5218.1

[ϕ] For this model: Akaike Corrected Information Criterion (AIC) = 1981.0; Bayesian Information Criterion (BIC) = 1984.9.

[†] Odds ratios from this multivariate analysis are adjusted for all the other covariates as listed in Table 2. For example, the adjusted odds ratio for clinicians' diagnosed exacerbation takes into account Fuchs' score ≥4, season, FEV_1 category, pancreatic status, *P. aeruginosa* and gender. Adjusted odds ratio >1 meant higher odds of clinicians recommending a course of IV during clinical reviews.

[‡] Odds ratios from this multivariate analysis are adjusted for all the other covariates as listed in Table 2. For example, the adjusted odds ratio for clinicians' diagnosed exacerbation takes into account Fuchs' score ≥4, season, FEV_1 category, pancreatic status, *P. aeruginosa* status and gender. Adjusted odds ratio >1 meant higher odds of adults with CF accepting a course of IV recommended by clinicians.

[¶] IV antibiotics were also used for non-exacerbation episodes, e.g. to arrest persistent FEV_1 decline due to uncontrolled chronic infection / inflammation.

[§] *P. aeruginosa* status was determined according to the Leeds criteria [34].

Clinicians recommended IV treatments in 388 (38.4%) of 1010 clinical encounters. A clinical diagnosis of exacerbation, presence of ≥4 Fuchs' features, encounters during winter, lower FEV_1, pancreatic insufficiency and presence of *P. aeruginosa* were independent predictors for IV recommendation by clinicians. The odds of IV recommendation were 80% higher (95% CI 12-179%) for adults with FEV_1 40-69.9% compared to FEV_1 ≥70%, even after taking into account a clinical diagnosis of exacerbation and symptom severity (see Table 2). Of 388 IV recommendations, 314 (80.9%) were accepted. Presence of ≥4 Fuchs' features, encounters during winter and lower FEV_1, but not clinicians' diagnosed exacerbations, were independent predictors for IV acceptance. The odds of IV acceptance were 148% higher (95% CI 40-412%) by adults with FEV_1 40-69.9% compared to FEV_1 ≥70% (see Table 2).

Contingency tables showing the distribution of covariates according to IV recommendations and acceptance, including all univariate analyses are available in Appendix A. The results in Table 2 are broadly similar to the results of sensitivity analyses for IV recommendations and acceptance following non-inpatient reviews (see Appendix B). Even after accounting for relevant presenting symptoms (worsening cough, new/worsening haemoptysis, new crackles on auscultation, acute FEV_1 decline [32]), baseline $\%FEV_1$ remains an important determinant of IV treatments for exacerbations (see Appendix C). The differential impact of $\%FEV_1$ on exacerbation rates and IV use is demonstrated in Appendix D. Among the subgroup of adults with objective nebuliser adherence data, there is a trend of increasing IV acceptance with increasing adherence levels (see Appendix E).

4. DISCUSSION

This study demonstrated that exacerbations are common, even among adults with relatively high baseline $\%FEV_1$. Many exacerbations (41.5%) were not IV treated, which is consistent with previous studies. ESCF data showed that only ~50% of exacerbations characterised by three/four Rabin criteria and ~2/3 of people with acute FEV_1 decline >10% were treated with additional antibiotics [9, 12]. We extended previous studies by explicitly collecting data of IV recommendation by clinicians and IV acceptance by adults with CF. We found that clinicians did not always recommend IV treatment for exacerbations and not all IV recommendations were accepted, but the factors associated with these decisions were somewhat different. Clinicians' diagnosis of exacerbation and CF prognostic markers (e.g. *P. aeruginosa* status) were associated with IV recommendations but not with IV acceptance. The difference may be partly due to clinicians only recommending IV treatments that are absolutely indicated and likely to be accepted. Yet 19% of all recommended IV courses were still declined, suggesting imperfect treatment targeting by clinicians. In all analyses, higher $\%FEV_1$ were associated with lower odds of IV recommendation by clinicians and IV acceptance by patients. Among clinicians, low baseline $\%FEV_1$ might be considered a risk factor for

treatment failure [35], hence the decision to recommend the most potent treatment. Among adults with CF, analyses in Appendix C suggest that IV acceptance is probably moderated by the experience and perception of symptoms, which can vary according to %FEV_1 [36]. Previous ESCF analyses have highlighted that less aggressive IV treatments of children with higher FEV_1 may contribute to accelerated FEV_1 decline [12, 14]. Our study showed that less aggressive IV treatments are influenced by both clinicians and people with CF. Therefore, attempts to improve outcomes by improving IV utilisation should focus on the behaviours of both clinicians and patients.

Our findings also suggest that directly capturing data regarding specific changes in clinical status that indicate an exacerbation may yield a more accurate epidemiological estimate of exacerbation frequencies. Current estimates are usually derived from CF registries or other medical databases e.g. commercial insurance databases [13, 37], which capture episodes of exacerbations indirectly by recording prescription of additional antibiotic treatments as a surrogate. Consequently, exacerbation events could only be captured if they were diagnosed and then triggered clinicians to offer treatments that were accepted by people with CF. Non-initiation of treatment does not necessarily indicate an absence of exacerbation, hence treatment data are likely to under-estimate exacerbation rates. Using treatment data as a surrogate may also result in spurious findings, since treatment data conflate differential treatment decisions and not all IV courses would be initiated for exacerbations. For example, 62.9% of IV courses were initiated during winter months yet only 48.6% of exacerbations occurred then.

Exacerbation is often used as an endpoint [3] and the limitations of treatment data as a surrogate in CF-related studies is worth considering. In blinded randomised drug trials, between-group differences in exacerbation treatments might be predominantly driven by differences in exacerbation rates. This may not be the case in observational studies where several factors can increase the recommendation and uptake of exacerbation treatments, even when the frequency and severity of exacerbations remain constant. A similar issue might arise in non-blinded trials where the evaluated interventions might influence behaviour. The therapeutic relationship between patients and the clinical team is likely to be a key ingredient influencing medication adherence [38, 39]. The rapport between patients and the clinical team is also likely to influence the uptake of IV treatments (which typically disrupt daily routine for ≥14 days). The analyses in Appendix E provided tentative evidence that adults with higher nebuliser adherence were more willing to accept IV recommendations. On the background of general under-recognition and under-treatment of exacerbations, better engagement could uncover many more exacerbations that were otherwise unrecognised. This is not to say that better engagement causes more exacerbations; the resultant increased detection or treatment of exacerbations is simply an example of ascertainment bias. This awareness is important when studying the relationships between medication adherence and health outcomes in CF.

A strength of this study is the low risk of selection bias with the inclusion of all eligible adults in Sheffield. This study does have several limitations. A single-centre study may lack generalisability

since there is between-centre variation in IV treatments [40]. Replication of findings with pre-specified analyses in larger prospectively collected datasets would be desirable. Nonetheless, our findings are consistent with previous studies (e.g. ESCF data also identified less aggressive IV treatment among people with higher FEV_1). It is also not possible to detect every exacerbation with 6-12 weekly clinic reviews. More exacerbations may well be detected with more intensive monitoring.[41] The exacerbation rates in our cohort (mean of 2.3 events/adult/year) is high, yet it is still likely to be an under-estimation. This does not necessarily diminish the significance of our findings. It is more likely for exacerbation events to be missed among those with higher FEV_1 (since people with lower FEV_1 are more symptomatic during exacerbations [14]), which means there could be even less discrepancy in exacerbation events between different $\%FEV_1$ categories in our cohort if exacerbations were not selectively missing. Another limitation is that exacerbation frequency does not account for the severity of each exacerbation event. A person on IV antibiotics continuously throughout the calendar year would only be considered to have a single exacerbation event and a single IV use episode based on the definition applied in this study. Counting sequential IV use separated by <7 days as a single episode (as per international convention [23, 42]) may selectively under-estimate both exacerbations and IV use among people with lower FEV_1, but it is unlikely to cause differential under-estimation of exacerbation events vs IV use episodes. We also did not examine the role of respiratory viruses (which have been shown to increase both the risk of exacerbations [43] and IV treatments [28]) and did not collect patient-reported symptoms in our study. It might be useful for future studies to explicitly screen patients for respiratory viruses and to use instruments such as the CF Respiratory Symptom Diary-Chronic Respiratory Infection Symptom Score (CRISS) [44] to collect data on patient-reported symptoms.

5. CONCLUSIONS

Exacerbations are common among adults with CF and a substantial proportion of these events may not be IV treated. In particular, people with higher FEV_1 were less aggressively treated with IV antibiotics due to both clinicians' and patients' decisions. Due to discrepancies between exacerbations and IV use, solely relying on IV episodes as an exacerbation surrogate will under-estimate the frequency of exacerbations and conceal differential treatment decisions according to varying clinical characteristics. Accurate measurement of exacerbations remains challenging because it relies on the recognition of these events in the absence of a universally accepted definition. An awareness of the current limitations in detecting exacerbations are important for clinical management and trial design in CF. More work is needed to determine how to capture the most pertinent data for detecting exacerbations and to streamline treatment decisions of exacerbations.

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Figure 1: the steps between exacerbation occurring and the initiation of IV antibiotics

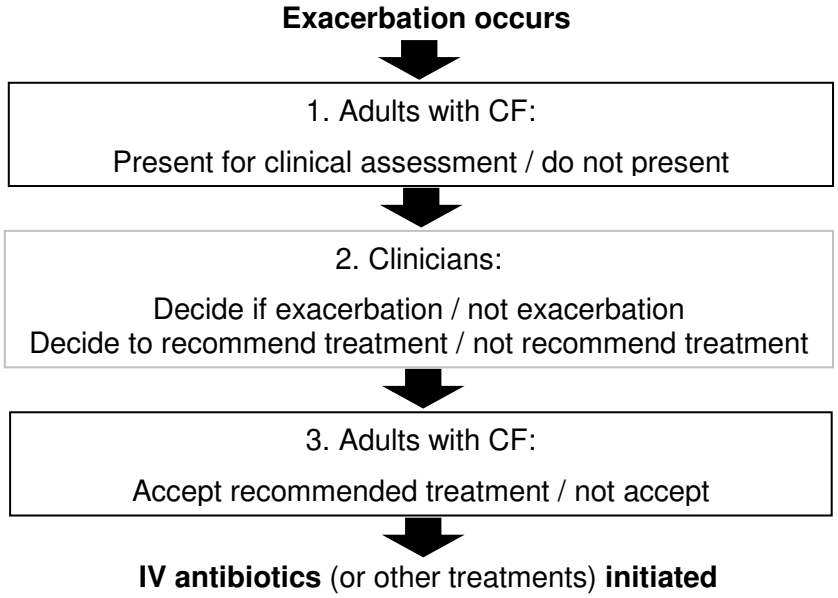
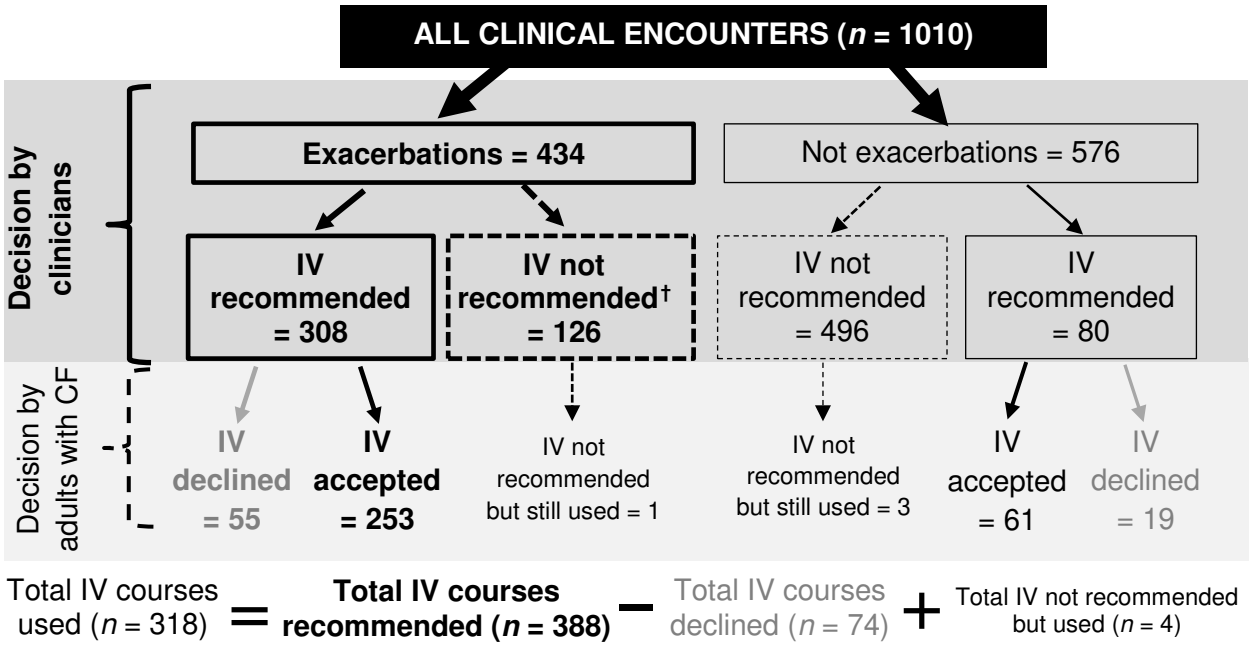
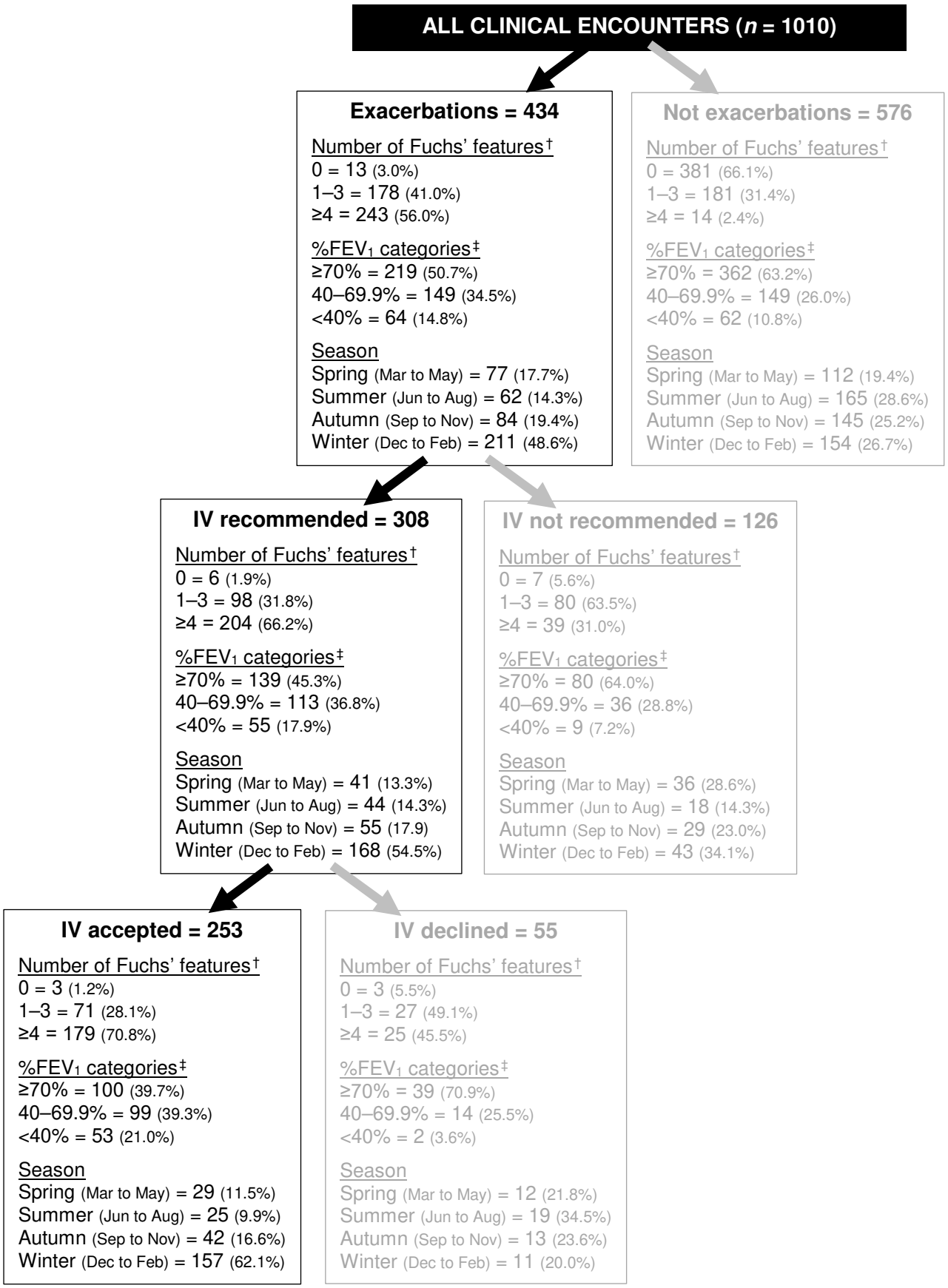


Figure 2: The relationship between exacerbation events and IV antibiotics use episodes



† In all episodes in which clinicians diagnosed exacerbations on clinical ground but felt IV treatments were not indicated, oral antibiotics were recommended instead.

Figure 3: Clinical parameters during clinical encounters¶ and the season of these encounters



¶ The figures presented do not account for correlated data from repeated measures within an individual.

† Exacerbations were diagnosed on clinical grounds by experienced CF physicians during all clinical reviews, although the diagnoses were guided by the Fuchs' criteria. A person with acute FEV_1 decline of up to 9% and otherwise reported no symptoms would have no Fuchs' feature, but could still be diagnosed as having an exacerbation.

‡ FEV_1 data were missing for five clinical encounters because a participant did not provide any $\%FEV_1$ readings due to the inability to perform spirometry.

Appendix A: Contingency tables showing the distribution of covariates listed in Table 2 of the main manuscript for all clinical encounters / IV recommendations, and results of the univariate analyses for the covariates

Table A.1: Contingency table and summary of results from the mixed-effects binary logistic regression model (random effect at individual level to account for repeated measures within an individual) for IV recommendation by clinicians among all 1010 clinical encounters (in 186 adults)

Covariates:	**Contingency table**† IV not recommended *n* = 622	IV recommended *n* = 388	**Results of the univariate analyses** Odds ratio‡ (95% CI)	P-value
Diagnosed as exacerbation by clinicians	126 (20.3%)	308 (79.4%)	**15.09 (10.72 to 21.25)**	**< 0.001**
Fuchs' score ≥4	47 (7.6%)	210 (54.1%)	**14.39 (9.73 to 21.29)**	**< 0.001**
Season of clinical encounter				**< 0.001**
Winter – Dec, Jan, Feb (reference category)	153 (24.6%)	212 (54.6%)	1 (Reference)	
Autumn – Sep, Oct, Nov	164 (26.4%)	65 (16.8%)	**0.31 (0.21 to 0.46)**	**< 0.001**
Summer – Jun, Jul, Aug	171 (27.5%)	56 (14.4%)	**0.25 (0.17 to 0.37)**	**< 0.001**
Spring – Mar, Apr, May	134 (21.5%)	55 (14.2%)	**0.32 (0.21 to 0.48)**	**< 0.001**
FEV_1 categories¶				**< 0.001**
≥70% (reference category)	412 (66.7%)	169 (43.7%)	1 (Reference)	
40 – 69.9%	153 (24.8%)	145 (37.5%)	**2.49 (1.62 to 3.83)**	**< 0.001**
<40%	53 (8.6%)	73 (18.9%)	**4.29 (2.31 to 7.97)**	**< 0.001**
Pancreatic insufficient	488 (78.5%)	370 (95.4%)	**5.99 (3.23 to 11.10)**	**< 0.001**
P. aeruginosa status				**< 0.001**
No *P. aeruginosa* (reference category)	284 (45.7%)	64 (16.5%)	1 (Reference)	
Intermittent *P. aeruginosa* infection	94 (15.1%)	67 (17.3%)	**3.13 (1.80 to 5.44)**	**< 0.001**
Chronic *P. aeruginosa* infection	244 (39.2%)	257 (66.2%)	**4.99 (3.28 to 7.61)**	**< 0.001**
Female	313 (50.3%)	223 (57.5%)	1.26 (0.84 to 1.88)	0.261

† The contingency table does not account for correlated data from repeated measures within an individual.

‡ Crude odds ratio presented for univariate analyses. Odds ratio >1 meant higher odds of clinicians recommending a course of IV during clinical reviews.

¶ One of the study subjects did not provide any $\%FEV_1$ readings due to the inability to perform spirometry, hence $\%FEV_1$ are missing for five of the clinical encounters (IV treatment was recommended in one of the encounters).

Table A.2: Contingency table and summary of results from the mixed-effects binary logistic regression model (random effect at individual level to account for repeated measures within an individual) for IV acceptance by adults with CF among all 388 recommended courses of IV (in 128 adults)

Covariates:	**Contingency table**† IV declined *n* = 74	IV accepted *n* = 314	**Results of the univariate analyses** Odds ratio‡ (95% CI)	P-value
Diagnosed as exacerbation by clinicians	55 (74.3%)	253 (80.6%)	1.51 (0.79 to 2.89)	0.217
Fuchs' score ≥4	27 (36.5%)	183 (58.3%)	**2.42 (1.37 to 4.28)**	**0.002**
Season of clinical encounter				**< 0.001**
Winter – Dec, Jan, Feb (reference category)	16 (21.6%)	196 (62.4%)	1 (Reference)	
Autumn – Sep, Oct, Nov	16 (21.6%)	49 (15.6%)	**0.28 (0.13 to 0.61)**	**0.002**
Summer – Jun, Jul, Aug	24 (32.4%)	32 (10.2%)	**0.12 (0.05 to 0.25)**	**< 0.001**
Spring – Mar, Apr, May	18 (24.3%)	37 (11.8%)	**0.19 (0.09 to 0.43)**	**< 0.001**
FEV_1 categories¶				**0.001**
≥70% (reference category)	48 (64.9%)	121 (38.7%)	1 (Reference)	
40 – 69.9%	23 (31.1%)	122 (39.0%)	**2.24 (1.15 to 4.35)**	**0.018**
<40%	3 (4.1%)	70 (22.4%)	**8.57 (2.36 to 31.07)**	**0.001**
Pancreatic insufficient	73 (98.6%)	297 (94.6%)	0.25 (0.03 to 2.12)	0.204
P. aeruginosa status				0.440
No *P. aeruginosa* (reference category)	13 (17.6%)	51 (16.2%)	1 (Reference)	
Intermittent *P. aeruginosa* infection	9 (12.2%)	58 (18.5%)	1.95 (0.63 to 6.08)	0.248
Chronic *P. aeruginosa* infection	52 (70.3%)	205 (65.3%)	1.07 (0.47 to 2.44)	0.864
Female	39 (52.7%)	184 (58.6%)	1.36 (0.71 to 2.59)	0.351

† The contingency table does not account for correlated data from repeated measures within an individual

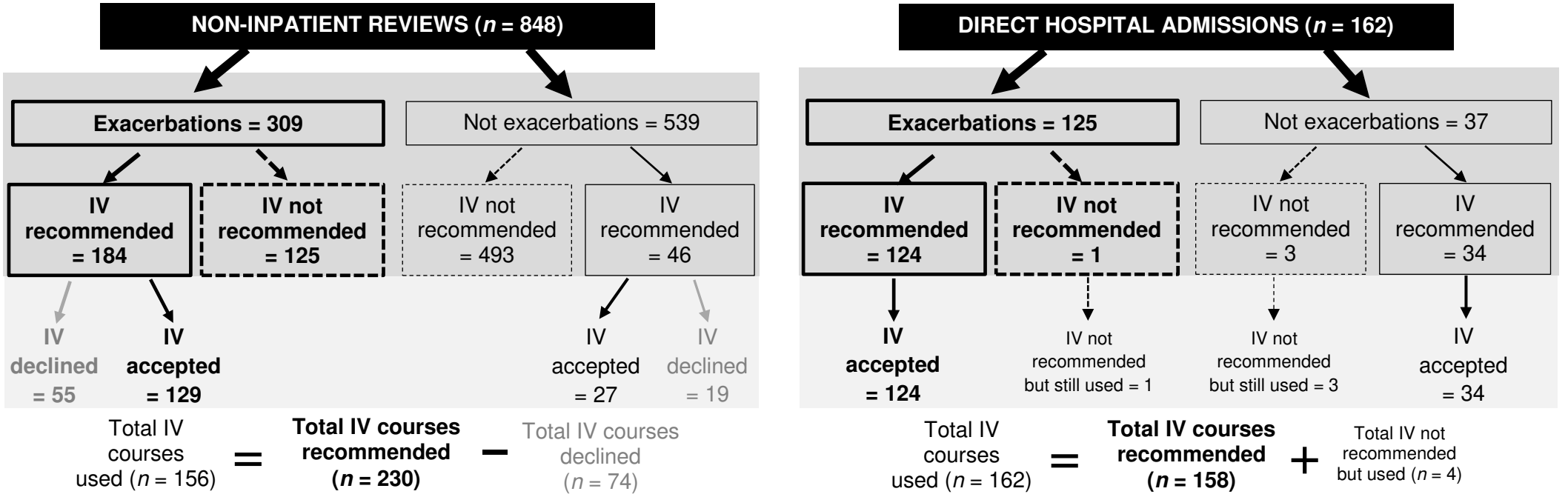
‡ Crude odds ratio presented for univariate analyses. Odds ratio >1 meant higher odds of adults with CF accepting a course of IV recommended by clinicians.

¶ One of the study subjects did not provide any $\%FEV_1$ readings due to the inability to perform spirometry, hence $\%FEV_1$ are missing for one of the recommended IV courses (IV recommendation was accepted in that encounter).

Appendix B: Sensitivity analyses of IV recommendation by clinicians and IV acceptance by adults with CF following non-inpatient reviews

Among the 318 IV courses used throughout 2016, 156 (49.1%) courses were initiated following non-inpatient reviews (e.g. routine outpatient clinics, ad hoc ward reviews and home visits) whilst the remaining courses were initiated for direct hospital admissions whereby IV treatments had already been pre-agreed prior to a face-to-face clinical review (see Figure B.1). It could be argued that decision making by clinicians and adults with CF during pre-agreed direct hospital admissions for IV treatments (in which the IV acceptance rate was 100%) may differ from non-inpatient reviews (in which IV treatments have not been pre-agreed, hence IV acceptance rate was only 68%).

Figure B.1: The relationship between exacerbation events and IV antibiotics use episodes, stratified according to the route of presentation



To understand the impact of IV courses that were initiated for direct hospital admissions on the results, the analyses reported in Table 2 of the main manuscript were repeated using only data from non-inpatient reviews (i.e. data from direct hospital admissions were excluded). These sensitivity analyses still showed broadly similar results to the analyses using data from all clinical encounters, with the only notable difference being the lack of seasonal influence (see Table B.1).

Table B.1: Summary of results from the multi-level mixed-effects binary logistic regression models (random effect at individual level, to account for repeated measures within an individual) for IV recommendation by clinicians and for IV acceptance by adults with CF following non-inpatient clinical reviews

	Comparing IV recommended vs IV not recommended by clinicians following 848 non-inpatient reviews (in 182 adults)[Ψ]		Comparing IV accepted vs IV not accepted by adults with CF among 230 recommended courses of IV following non-inpatient reviews (in 108 adults)[ϕ]	
Predictors	Adjusted odds ratio[†] (95% CI)	P-value	Adjusted odds ratio[‡] (95% CI)	P-value
Diagnosed as exacerbation by clinicians	**9.84 (6.10 to 15.87)**	**< 0.001**	1.17 (0.50 to 2.75)	0.715
Fuchs' score ≥4	**4.11 (2.43 to 6.95)**	**< 0.001**	**2.77 (1.34 to 5.72)**	**0.006**
Season of clinical encounter (Winter as reference)		0.585		0.342
Autumn – Sep, Oct, Nov	1.22 (0.69 to 2.15)	0.499	1.00 (0.40 to 2.50)	1.000
Summer – Jun, Jul, Aug	1.49 (0.82 to 2.71)	0.186	0.50 (0.21 to 1.22)	0.125
Spring – Mar, Apr, May	1.09 (0.60 to 1.98)	0.769	0.74 (0.29 to 1.87)	0.520
FEV_1 categories (≥70% as reference)		0.082		**0.031**
40 – 69.9%	**1.67 (1.01 to 2.77)**	**0.047**	**2.22 (1.03 to 4.77)**	**0.042**
<40%	0.80 (0.34 to 1.88)	0.611	**4.79 (1.11 to 20.61)**	**0.036**
Pancreatic insufficient	**6.49 (2.82 to 14.92)**	**< 0.001**	0.33 (0.04 to 3.11)	0.334
P. aeruginosa status (no *P. aeruginosa* as reference)		**0.007**		0.093
Intermittent *P. aeruginosa* infection	**2.67 (1.31 to 5.45)**	**0.007**	1.44 (0.42 to 4.88)	0.560
Chronic *P. aeruginosa* infection	**2.19 (1.25 to 3.83)**	**0.006**	0.52 (0.21 to 1.29)	0.156
Female	0.87 (0.54 to 1.41)	0.570	1.03 (0.50 to 2.11)	0.941

[Ψ] For this model: Akaike Corrected Information Criterion (AIC) = 4405.0; Bayesian Information Criterion (BIC) = 4409.7. Of the 848 non-inpatient reviews, IV was recommended on 230 (27.1%) occasions and not recommended on 618 (72.9%) occasions.

[ϕ] For this model: Akaike Corrected Information Criterion (AIC) = 1037.6; Bayesian Information Criterion (BIC) = 1040.9. Of the 230 IV recommendations following non-inpatient reviews, IV was accepted on 156 (67.8%) occasions and declined on 74 (32.2%) occasions.

[†] Odds ratios from this multivariate analysis are adjusted for all the other covariates as listed in Table B.1. For example, the adjusted odds ratio for clinicians' diagnosed exacerbation takes into account Fuchs' score ≥4, season, FEV_1 category, pancreatic status, *P. aeruginosa* status and gender. Adjusted odds ratio >1 meant higher odds of clinicians recommending a course of IV during clinical reviews.

[‡] Odds ratios from this multivariate analysis are adjusted for all the other covariates as listed in Table B.1. For example, the adjusted odds ratio for clinicians' diagnosed exacerbation takes into account Fuchs' score ≥4, season, FEV_1 category, pancreatic status, *P. aeruginosa* status and gender. Adjusted odds ratio >1 meant higher odds of adults with CF accepting a course of IV recommended by clinicians.

Clinicians recommended IV treatments in 230 (27.1%) of the 848 non-inpatient reviews. A clinical diagnosis of exacerbation, presence of ≥4 Fuchs' features, lower FEV_1, pancreatic insufficiency and presence of *P. aeruginosa* in respiratory cultures were independent predictors for IV recommendations by clinicians. The odds of clinicians recommending IV treatments were 67%

higher (95% CI 1% to 177%) for an adult with FEV_1 40-69.9% compared to an adult with FEV_1 ≥70%, even after taking into account the presence of exacerbations and symptom severity. Of the 230 IV recommendations following non-inpatient reviews, 156 (67.8%) were accepted. Presence of ≥4 Fuchs' features and lower FEV_1, but not clinicians' diagnosed exacerbation, were independent predictors for IV acceptance by adults with CF. The odds of IV acceptance were 122% higher (95% CI 3% to 377%) among adults with FEV_1 40-69.9% compared to adults with FEV_1 ≥70%. Therefore, FEV_1 still influenced clinicians' and patients' decisions regarding IV treatments following non-inpatient reviews.

Appendix C: Sensitivity analyses to take into account clinical features which influence the treatment of pulmonary exacerbations

A previous analysis using Epidemiologic Study of CF (ESCF) data found that the four clinical characteristics most associated with treatment of pulmonary exacerbations among adults with CF are decline in $\%FEV_1$, new crackles on auscultation, haemoptysis and increased cough [1]. Another ESCF analysis, which showed that children with higher FEV_1 were less likely to be treated with IV antibiotics following an acute FEV_1 decline, was repeated among children with daily cough, daily sputum production and crackles on auscultation at the visit closest to acute FEV_1 decline as a sensitivity analysis since these are the most relevant clinical characteristics in the treatment of exacerbations among children with CF [2]. Only one exacerbation event in our cohort was associated with the combination of acute FEV1 decline of ≥10%, change in chest auscultation, new / increased haemoptysis and increased cough. Therefore, it is not possible to restrict analysis of exacerbation treatments to the events when all relevant clinical characteristics were present. Instead we repeated our main analysis using multi-level mixed-effects binary logistic regression models but fitted these clinical characteristics as fixed effect along with $\%FEV_1$ categories.

The aim of this sensitivity analysis is to determine if $\%FEV_1$ was still independently associated with increased odds of clinicians recommending IV to treat exacerbations and adults with CF accepting those recommended IV courses. This analysis was restricted to exacerbation events only because symptoms most relevant to the treatment of pulmonary exacerbations are unlikely to drive treatment decisions of non-exacerbation events. Fuchs' features were used for this sensitivity analysis, hence the minor differences compared to the clinical characteristics available in the ESCF dataset. For example, "absolute FEV_1 decreased by ≥10% compared to previous recorded value" was collected from our cohort as part of the Fuchs' feature but relative decline of ≥15% was the optimal cut-off in the ESCF dataset [1].

In our cohort, clinicians recommended IV treatments in 308 (71.0%) of the 434 detected exacerbation events. Presence of ≥4 Fuchs' features, encounters during winter, pancreatic insufficiency, presence of *P. aeruginosa* in respiratory cultures and lower FEV_1 were independent predictors for IV recommendations by clinicians to treat pulmonary exacerbations. After taking into account the four most relevant clinical characteristics that influence treatment of exacerbations among adults with CF [1], the odds of clinicians recommending IV treatments were 227% higher (95% CI 28% to 738%) for an adult with FEV_1 <40% compared to an adult with FEV_1 ≥70% (see Table C.1). Of the 308 IV recommendations for treatment of exacerbations, 253 (82.1%) were accepted by adults with CF in our cohort. Presence of ≥4 Fuchs' features, encounters during winter and lower FEV_1 were independent predictors for IV acceptance. However, $\%FEV_1$ did not quite achieve statistical significance (p = 0.053) after taking into account the four most relevant clinical characteristics that influence treatment of exacerbations among adults with CF [1]. Nonetheless, there was still a clear trend of increasing odds for IV acceptance with lower $\%FEV_1$ (see Table C.1). For example, the odds of IV acceptance for exacerbations were 357% higher (95% CI 10% lower to 2207% higher) among adults with FEV_1 <40% compared to those with FEV_1 ≥70%.

Table C.1: Summary of results from the multi-level mixed-effects binary logistic regression models (random effect at individual level, to account for repeated measures within an individual) for IV recommendation by clinicians and for IV acceptance by adults with CF for treatment of pulmonary exacerbations

Predictors	Comparing IV recommended vs IV not recommended by clinicians to treat pulmonary exacerbations (in 150 adults)[Ψ]		Comparing IV accepted vs IV not accepted by adults with CF among 308 recommended courses of IV to treat exacerbations (in 116 adults)[ϕ]	
	Adjusted odds ratio[†] (95% CI)	P-value	Adjusted odds ratio[‡] (95% CI)	P-value
Covariates for the main analyses				
Fuchs' score ≥4	**4.71 (2.88 to 7.73)**	**< 0.001**	**3.64 (1.69 to 7.84)**	**0.001**
Season of clinical encounter (Winter as reference)		**< 0.001**		**< 0.001**
Autumn – Sep, Oct, Nov	**0.34 (0.18 to 0.62)**	**0.001**	**0.20 (0.08 to 0.53)**	**0.001**
Summer – Jun, Jul, Aug	**0.22 (0.11 to 0.45)**	**< 0.001**	**0.10 (0.04 to 0.25)**	**< 0.001**
Spring – Mar, Apr, May	**0.18 (0.09 to 0.34)**	**< 0.001**	**0.15 (0.05 to 0.42)**	**< 0.001**
FEV_1 categories (≥70% as reference)		**0.006**		**0.007**
40 – 69.9%	**2.21 (1.30 to 3.76)**	**0.004**	**3.05 (1.28 to 7.23)**	**0.012**
<40%	**2.38 (1.03 to 5.51)**	**0.043**	**7.40 (1.38 to 39.59)**	**0.020**
Pancreatic insufficient	**4.76 (2.08 to 10.91)**	**< 0.001**	0.47 (0.05 to 4.52)	0.511
P. aeruginosa status (no *P. aeruginosa* as reference)		**0.009**		0.198
Intermittent *P. aeruginosa* infection	**3.55 (1.58 to 7.94)**	**0.002**	2.05 (0.50 to 8.51)	0.320
Chronic *P. aeruginosa* infection	1.50 (0.83 to 2.71)	0.180	0.67 (0.24 to 1.88)	0.450
Female	0.93 (0.56 to 1.53)	0.760	0.69 (0.31 to 1.55)	0.366
Clinical presentations as the covariates				
FEV_1 categories (≥70% as reference)		**0.027**		0.053
40 – 69.9%	1.67 (0.91 to 3.08)	0.100	2.42 (0.98 to 5.16)	0.066
<40%	**3.27 (1.28 to 8.38)**	**0.013**	4.57 (0.90 to 23.07)	0.057
Absolute FEV_1 decline by ≥10% compared to previous recorded value	**6.24 (2.96 to 13.13)**	**< 0.001**	**0.40 (0.20 to 0.79)**	**0.009**
Change in chest auscultation	**4.64 (2.17 to 9.93)**	**< 0.001**	**3.23 (1.22 to 8.58)**	**0.019**
New / increased haemoptysis	1.46 (0.58 to 3.67)	0.423	1.00 (0.34 to 2.95)	0.993
Increase in cough	**2.00 (1.07 to 3.75)**	**0.030**	**3.72 (1.56 to 8.89)**	**0.003**

[Ψ] For the model with covariates from the main analysis: Akaike Corrected Information Criterion (AIC) = 2045.9; Bayesian Information Criterion (BIC) = 2050.0. For the model which included clinical presentations as covariates: Akaike Corrected Information Criterion (AIC) = 2053.8; Bayesian Information Criterion (BIC) = 2057.8.

[ϕ] For the model with covariates from the main analysis: Akaike Corrected Information Criterion (AIC) = 1589.7; Bayesian Information Criterion (BIC) = 1593.4. For the model which included clinical presentations as covariates: Akaike Corrected Information Criterion (AIC) = 1564.7; Bayesian Information Criterion (BIC) = 1568.4.

[†] Odds ratios from these multivariate analyses are adjusted for all the other covariates as listed in the relevant row of Table C.1. For example, in the analysis using clinical presentations as covariates, the adjusted odds ratio for FEV_1 category takes into account FEV_1 decline by ≥10%, change in chest auscultation, new / increased haemoptysis and increase in cough. Adjusted odds ratio >1 meant higher odds of clinicians recommending a course of IV to treat a clinician-diagnosed exacerbation.

[‡] Odds ratios from these multivariate analyses are adjusted for all the other covariates as listed in the relevant row of Table C.1. For example, in the analysis using clinical presentations as covariates, the adjusted odds ratio for FEV_1 category takes into account FEV_1 decline by ≥10%, change in chest auscultation, new / increased haemoptysis and increase in cough. Adjusted odds ratio >1 meant higher odds of adults with CF accepting a course of IV that was recommended for the treatment of a clinician-diagnosed exacerbation.

In keeping with the ESCF analysis [1], these results suggest that clinical characteristics of pulmonary exacerbations have an important impact on treatment decisions. However, the relative importance of specific clinical characteristics were perhaps perceived differently by clinicians and adults with CF. For example, a substantial (≥10%) acute FEV_1 decline increased the odds of clinicians recommending IV treatments but did not prompt treatment acceptance by adults with CF. This may partly be due to appropriate treatment targeting by clinicians, such that clinical characteristics of exacerbations no longer influence the decisions by adults with CF. However, 55 (17.9%) of the recommended IV courses were still turned down and this included 29 (52.7%) occasions in which there were ≥10% absolute decline in FEV_1 compared to previous readings. Therefore, the reduced odds of adults accepting IV in the face of substantial acute FEV_1 decline probably reflect the fact that such decline was more likely among adults with high FEV_1 (among 104 of such events during exacerbations, 63 i.e. 60.6% of these occurred among adults with FEV_1 ≥70%). Adults with high FEV_1 are probably less likely to perceive symptoms from acute FEV_1 decline and are also more likely to turn down recommended IV courses. Indeed, previous studies indicated that adults with CF perceived exacerbation differently according to $\%FEV_1$ categories [3] and also have different perspective of what constitutes an “exacerbation” compared to clinicians [4].

In summary, this sensitivity analyses indicate that clinicians were still more likely to recommend IV treatments for exacerbations among adults with lower baseline $\%FEV_1$ regardless of presenting symptoms / characteristics. There was also a trend of adults with a lower $\%FEV_1$ being more likely to accept IV treatments for exacerbations, although their decisions were more strongly moderated by the presenting symptoms / characteristics. Previous qualitative studies have suggested that treatment decisions by adults with CF are influenced by the symptoms they experienced and their perception of those symptoms [5, 6], since IV antibiotics can also cause systemic side-effects which are distressing [7, 8].

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Appendix D: A further analysis to explore the impact of %FEV_1 on the frequencies of exacerbation events and IV use episodes

Given the analyses in the main manuscript, Appendix B and Appendix C have consistently demonstrated preferential use of IV antibiotics among people with lower %FEV_1, it is worth exploring the discrepancies between exacerbations and IV use against %FEV_1. Therefore, a negative binomial regression model was used to compare exacerbation and IV use frequency for the same %FEV_1 categories used in the other analyses. As discussed in the main manuscript, a negative binomial regression model was used due to its suitability in handling count data with over-dispersion.

This analysis showed substantial increase in IV use episodes with lower %FEV_1, but the increase in exacerbation events was less obvious. There were overlapping confidence intervals for the exacerbation event rates among adults with lowest and highest %FEV_1, and even those with FEV_1 ≥70% had ~2 exacerbation events/year (see Table D.1).

Table D.1: Exacerbations and IV use episodes for different %FEV_1 categories

	Clinicians' diagnosed exacerbation events			**IV antibiotics use episodes**		
%FEV_1 categories †	≥70% (*n* = 116)	40 – 69.9% (*n* = 51)	<40% (*n* = 18)	≥70% (*n* = 116)	40 – 69.9% (*n* = 51)	<40% (*n* = 18)
Number of event(s), *n* (%)						
0	27 (23.3)	8 (15.7)	1 (5.6)	54 (46.5)	8 (15.7)	1 (5.6)
1	32 (27.6)	8 (15.7)	3 (16.7)	35 (30.2)	10 (19.6)	2 (11.1)
2	27 (23.3)	8 (15.7)	1 (5.6)	11 (9.5)	13 (25.5)	3 (16.7)
3	12 (10.3)	8 (15.7)	5 (27.8)	6 (5.2)	9 (17.6)	1 (5.6)
4	6 (5.2)	6 (11.8)	2 (11.1)	3 (2.6)	3 (5.9)	3 (16.7)
≥5	12 (10.3)	13 (25.5)	6 (33.3)	7 (6.0)	8 (15.7)	8 (44.4)
Results from the negative binomial regression model:						
Event rate (95% CI)	1.9 (1.5 to 2.4)	2.9 (2.1 to 4.0)	3.6 (2.1 to 6.0)	1.1 (0.8 to 1.4)	2.4 (1.7 to 3.3)	3.9 (2.4 to 6.6)
Rate ratio ‡ (95% CI)	1 (Reference)	1.55 (1.05 to 2.28)	1.89 (1.07 to 3.33)	1 (Reference)	2.24 (1.48 to 3.38)	3.69 (2.08 to 6.56)
P-value for the rate ratio	–	0.028	0.029	–	< 0.001	< 0.001
Overall event rate		2.3 (2.0 to 2.8)			1.7 (1.4 to 2.1)	
Overall P-value		0.043			< 0.001	

† One of the study subjects did not provide any %FEV_1 readings due to the inability to perform spirometry

‡ Rate ratio >1 meant higher exacerbation rates.

This analysis highlights the limitations of using treatment data as a surrogate for exacerbation events. Excess IV use among people with lower FEV_1 is not just due to increased exacerbation rates but also conflates differential treatment decisions according to FEV_1. The discrepancy between exacerbations and IV treatments may result in the misconception that the risk of exacerbations substantially increases with reduced %FEV_1 when in fact, it is the probability of IV treatments that substantially increases with reduced %FEV_1.

Appendix E: A subgroup analysis of IV acceptance by adults with objective nebuliser adherence data

Among the 186 adults with CF included in the main analyses, 102 (54.8%) adults were using I-neb® (which is a tamper-proof intelligent nebuliser machine that automatically and accurately logs every time a drug is being nebulised) as part of their routine treatment. Objective nebuliser adherence data are therefore available for this subgroup. This is an interesting subgroup to study because adherence may be a proxy for the rapport between adults with CF and the clinical team (various studies have suggested that medication adherence is influenced by the therapeutic relationship between patients and their clinical teams [1-3]), and this rapport may also influence IV acceptance by adults with CF.

I-neb® is typically reserved for people who require nebulised antibiotics. In comparison to those not on I-neb®, adults on I-neb® had more severe phenotype as evidenced by lower %FEV_1 and a higher proportion of pancreatic insufficiency (see Table E.1). This suggests appropriate targeting of I-neb® use for those with more severe lung disease, hence the higher IV use and exacerbation rates.

Table E.1: Demographic and clinical characteristics of the adults using vs not using I-neb®

	Adults on I-neb® (*n* = 102)	Adults not on I-neb® (*n* = 84)
Age in years, median (IQR)	26 (20 to 32)	28 (22 to 35)
Female, *n* (%)	42 (41.2)	48 (57.1)
Genotype status:		
≥1 unknown mutation(s), *n* (%)	2 (2.0)	13 (15.5)
≥1 class IV-V mutation(s), *n* (%)	9 (8.8)	25 (29.8)
Homozygous class I-III, *n* (%)	91 (89.2)	46 (54.8)
Pancreatic insufficient, *n* (%)	95 (93.1)	50 (59.5)
CF related diabetes, *n* (%)	32 (31.4)	22 (26.2)
P. aeruginosa status:		
No *P. aeruginosa*, *n* (%)	33 (32.4)	45 (53.6)
Intermittent *P. aeruginosa*, *n* (%)	20 (19.6)	9 (10.7)
Chronic *P. aeruginosa*, *n* (%)	49 (48.0)	30 (35.7)
BMI, median (IQR)	23.2 (20.6 to 25.4)	23.2 (20.0 to 27.4)
Best %FEV_1,¶ median (IQR)	76.4 (62.1 to 87.0)	80.8 (55.3 to 91.6)
IV days		
Median (IQR)	18 (0 to 42)	10 (0 to 33)
Mean (95% CI)ϕ	26.9 (22.1 to 32.8)	25.4 (20.4 to 31.5)
IV use episodes,		
0, *n* (%)	29 (28.4)	34 (40.5)
1, *n* (%)	27 (26.5)	21 (25.0)
2, *n* (%)	18 (17.6)	9 (10.7)
3, *n* (%)	11 (10.8)	5 (6.0)
4, *n* (%)	6 (5.9)	3 (3.6)
≥5, *n* (%)	11 (10.8)	12 (14.3)
Mean (95% CI)ϕ	1.8 (1.4 to 2.3)	1.6 (1.3 to 2.2)
Exacerbation events		
0, *n* (%)	13 (12.7)	23 (27.4)
1, *n* (%)	24 (23.5)	19 (22.6)
2, *n* (%)	19 (18.6)	18 (21.4)
3, *n* (%)	16 (15.7)	9 (10.7)
4, *n* (%)	11 (10.8)	3 (3.6)
≥5, *n* (%)	19 (18.6)	12 (14.3)
Mean (95% CI)ϕ	2.6 (2.1 to 3.3)	2.0 (1.5 to 2.6)

¶ One of the study subjects not on I-neb® did not provide any %FEV_1 readings due to the inability to perform spirometry.

ϕ The mean and 95% confidence intervals are calculated using a negative binomial regression model.

Clinicians recommended IV treatments in 232 (40.6%) of the 572 clinical encounters with adults using I-neb®. Of the 232 IV recommendations, 179 (77.2%) were accepted by adults using I-neb®. In this subgroup, the presence of more symptoms did not achieve statistical significance in terms of independently predicting IV acceptance (p = 0.066), although the adjusted odds ratio of 2.22 were similar to the overall cohort (see Table E.2). Winter season and lower FEV_1 remained as independent predictors for IV acceptance.

Table E.2: Summary of results from the multi-level mixed-effects binary logistic regression models (random effect at individual level to account for repeated measures within an individual) for IV acceptance by adults with CF using I-neb®, including and excluding adherence as one of the covariates

	Comparing IV accepted vs IV not accepted by adults with CF using I-neb® among 232 recommended courses of IV (in 78 adults)Ψ, adherence not included as a covariate		Comparing IV accepted vs IV not accepted by adults with CF using I-neb® among 232 recommended courses of IV (in 78 adults)ϕ, **adherence included as a covariate**	
Predictors	Adjusted odds ratio† (95% CI)	P-value	Adjusted odds ratio† (95% CI)	P-value
Diagnosed as exacerbation by clinicians	2.08 (0.76 to 5.70)	0.154	2.44 (0.86 to 6.94)	0.094
Fuchs' score ≥4	2.22 (0.95 to 5.22)	0.066	2.37 (0.99 to 5.69)	0.053
Season of clinical encounter (Winter as reference)		**0.001**		**0.001**
Autumn – Sep, Oct, Nov	**0.32 (0.11 to 0.94)**	**0.039**	**0.32 (0.11 to 0.97)**	**0.044**
Summer – Jun, Jul, Aug	**0.14 (0.06 to 0.38)**	**< 0.001**	**0.13 (0.05 to 0.35)**	**< 0.001**
Spring – Mar, Apr, May	**0.25 (0.09 to 0.70)**	**0.008**	**0.25 (0.09 to 0.71)**	**0.009**
FEV_1 categories (≥70% as reference)		**0.013**		**0.014**
40 – 69.9%	**3.37 (1.33 to 8.54)**	**0.011**	**3.55 (1.37 to 9.18)**	**0.009**
<40%	**6.66 (1.04 to 42.50)**	**0.045**	6.17 (0.91 to 41.78)	0.062
Pancreatic insufficient	N/A¶		N/A¶	
P. aeruginosa status (no *P. aeruginosa* as reference)		0.473		0.475
Intermittent *P. aeruginosa* infection	1.33 (0.34 to 5.30)	0.681	1.42 (0.35 to 5.73)	0.623
Chronic *P. aeruginosa* infection	0.67 (0.23 to 2.00)	0.474	0.70 (0.23 to 2.10)	0.520
Female	1.09 (0.46 to 2.62)	0.840	1.21 (0.50 to 2.94)	0.672
Normative adherence clusters‡ ('Cluster 1', i.e. very low adherence, as reference)	N/A			0.149
'Cluster 2' – low adherence			0.82 (0.28 to 2.38)	0.708
'Cluster 3' – moderate adherence			1.96 (0.66 to 5.85)	0.225
'Cluster 4' – high adherence			3.52 (0.82 to 15.11)	0.091

Ψ For this model: Akaike Corrected Information Criterion (AIC) = 1124.0; Bayesian Information Criterion (BIC) = 1127.4. Of the 232 IV recommendations for adults using I-neb®, IV was accepted on 179 (77.2%) occasions and declined on 53 (22.8%) occasions.

ϕ For this model: Akaike Corrected Information Criterion (AIC) = 1142.1; Bayesian Information Criterion (BIC) = 1145.5. Of the 232 IV recommendations for adults using I-neb®, IV was accepted on 179 (77.2%) occasions and declined on 53 (22.8%) occasions.

† Odds ratios from these multivariate analyses are adjusted for all the other covariates as listed in Table E.2. For example, the adjusted odds ratio for adherence clusters takes into account clinicians' diagnosed exacerbation, Fuchs' score ≥4, season, FEV_1 category, *P. aeruginosa* status and gender. Adjusted odds ratio >1 meant higher odds of adults with CF using I-neb® accepting a course of IV recommended by clinicians.

‡ Objective adherence data from 1st January 2016 to 31st December 2016 were downloaded from I-neb® and calculated as 'normative adherence'. 'Normative adherence' takes into account a person's characteristics when defining the minimum required treatment regimen [4]. Calculation of 'normative adherence' involves adjusting the denominator according to *P. aeruginosa* status, adjusting the numerator by capping daily maximum nebuliser use at 100% (also accounting for doses taken after midnight), adjusting the numerator for incomplete doses, adjusting the numerator for device dose delivery characteristics and adjusting the numerator by accounting for dose spacing of inhaled antibiotics. A person with chronic *P. aeruginosa* infection should take at least a nebulised mucolytic and an antibiotic. Thus the denominator for a person with chronic *P. aeruginosa* infection will be at least 3 (1x dornase alfa, 2x antibiotic). If a person with chronic *P. aeruginosa* infection only agreed to use nebulised dornase alfa once daily (which is 1 nebuliser/day), even if they take every dose of their dornase alfa, the 'normative adherence' is only 33%. The detailed methods and worked examples of calculating 'normative adherence' are provided in the paper by Hoo et al [4]. Following the calculation of 'normative adherence', adherence data were then clustered according to previously described methods [5] on a 3-monthly basis (Jan-Mar 2016, Apr-Jun 2016, Jul-Sep 2016, Oct-Dec 2016).

¶ Odds ratio for pancreatic status could not be estimated in the logistic regression model because every adult using I-neb® and accepting IV recommendations was pancreatic insufficient.

Therefore, there were similarities with the overall cohort in terms of the factors that influenced IV acceptance although the subgroup of adults using I-neb® have more severe phenotype and lung disease. In this subgroup, there were higher adjusted odd ratios of accepting IV recommendations among adults with moderate and high adherence levels, although these did not meet statistical significance ($p = 0.149$). The odds of IV acceptance were 252% higher (95% CI 28% lower to 1411% higher) among the subgroup of adults with high adherence ('Cluster 4') compared to those with the lowest adherence level ('Cluster 1'). The very wide confidence intervals indicate that the sample size is too small to reliably detect a difference even though the effect size may be very large and clinically important. The multi-level model also had fewer than 10 events per covariate (53 IV rejections, seven covariates), which may bias the results [6]. Higher odds of IV acceptance with higher adherence levels were also observed in a univariate mixed-effects binary logistic regression model (see Table E.3). Therefore, this subgroup analysis has generated an interesting hypothesis that can be further tested in larger prospective datasets.

Table E.3: Contingency table and summary of results from the mixed-effects binary logistic regression model (random effect at individual level to account for repeated measures within an individual) for IV acceptance by the subgroup of adults with CF using I-neb®

	Contingency table†		**Results of the univariate analyses**	
Covariate of interest:	IV declined *n* = 53	IV accepted *n* = 179	Odds ratio‡ (95% CI)	P-value
Normative adherence clusters:				0.334
'Cluster 1' – very low adherence	19 (35.8%)	55 (30.7%)	1 (Reference)	
'Cluster 2' – low adherence	16 (30.2%)	38 (21.2%)	0.71 (0.28 to 1.80)	0.467
'Cluster 3' – moderate adherence	13 (24.5%)	52 (29.1%)	1.47 (0.54 to 3.99)	0.448
'Cluster 4' – high adherence	5 (9.4%)	34 (19.0%)	1.98 (0.56 to 6.94)	0.285

† The contingency table does not account for correlated data from repeated measures within an individual.

‡ Crude odds ratio presented for this univariate analysis. Odds ratio >1 meant higher odds of adults with CF using I-neb® accepting a course of IV recommended by clinicians.

Given the possibility that willingness to accept IV recommendations may increase as adherence levels improve, methods to study the relationships between medication adherence and pulmonary exacerbation (which is an important health outcome in CF) should be carefully considered. If antibiotics treatment was used as a surrogate for an exacerbation, it may be possible to observe "increases in exacerbation rates" which simply reflect increases in treatment uptake rather than actual deterioration of lung health. For accurate elucidation of the relationships between medication adherence and exacerbations, it may be preferable to study clinical presentations consistent with exacerbations instead of using treatment data as the proxy.

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