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Title: A comparison of the CFHH criteria against the Leeds criteria in determining the Pseudomonas aeruginosa status among adults with cystic fibrosis

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ABSTRACT

Background

Pseudomonas aeruginosa (PA) status influences management decisions in cystic fibrosis (CF) but diagnostic approaches vary. We evaluated the ability of the CFHH criteria, which consist of two major and four minor statements, in diagnosing chronic PA infection among adults with CF.

Methods

In this retrospective cross-sectional analysis, we compared the CFHH criteria against the Leeds criteria. Data were collected between 1st January and 31st December 2016 from all adults with CF receiving care at Sheffield, excluding those with lung transplantation (*n*=7) or on ivacaftor (*n*=13). The CFHH criteria PA status were cross-tabulated against the Leeds criteria, and clinical outcomes between chronic PA vs non chronic PA for both criteria were compared.

Results

This analysis included 186 adults with CF (90 females, median age 27 years, median baseline FEV_1 78.5%). The CFHH criteria diagnosed more cases of chronic PA (116/186, 62.4% vs 79/186, 42.5%), and 37/107 cases of non-chronic PA according to the Leeds criteria were deemed chronic PA by the CFHH criteria. The magnitude of difference in $\%FEV_1$ decline between chronic PA vs non chronic PA was slightly greater for the CFHH criteria (–0.6%, 95% CI –1.8 to 0.6%) compared to the Leeds criteria (–0.2%, 95% CI –1.3 to 1.0%).

Conclusions

The CFHH criteria detected more cases chronic PA yet still retained similar levels of discrimination for health outcomes in comparison to the Leeds criteria. These findings provide preliminary evidence for the validity of the CFHH criteria among adults with CF.

KEYWORDS:

Cystic fibrosis; Pseudomonas aeruginosa; Classification; Evaluation studies

INTRODUCTION

Cystic fibrosis (CF) is a genetic life-limiting long-term condition characterised by increased susceptibility to recurrent lung infections by resistant pathogens, which leads to progressive lung damage and respiratory failure [1]. An important CF lung pathogen is *Pseudomonas aeruginosa* (PA). It is the most prevalent chronic pathogen among adults with CF [2] and once acquired, it is associated with worse prognosis in terms of accelerated $\%FEV_1$ decline and increased pulmonary exacerbation rates [3]. PA status influences various clinical decisions including clinical segregation, the choice of preventative inhaled therapies and the choice of intravenous antibiotics to treat exacerbations [4]. Accurate determination of PA status is therefore important in the management of people with CF. For example, long-term inhaled antibiotics which reduce the risk of exacerbation and improve $\%FEV_1$ among people with chronic PA infection [5] may not be initiated if that diagnosis was missed.

The most commonly used definition for PA status in CF epidemiological research is the Leeds criteria. Chronic PA infection according to the Leeds criteria requires >50% of months in the preceding 12 months with respiratory samples that were positive for PA [4]. Thus the Leeds criteria set a high threshold for the diagnosis of chronic PA infection, creating criteria that are very specific. For example, if an adult provided nine sputum samples over seven months in the previous year and PA was cultured in three of those months, that person would not be diagnosed as chronic PA according to the Leeds criteria even if most of the samples (e.g. five of nine) were PA positive. However, studies have demonstrated that the Leeds criteria are insensitive with a tendency to mis-diagnose chronic PA as intermittent infection [6, 7]. The major clinical guidelines in CF [5, 8, 9] do not define PA status according to the Leeds criteria; and definitions of PA status in clinical trials targeting adults with chronic PA infection have used various definitions [10]. Clinicians are also unlikely to use the Leeds criteria in their day-to-day work. Our previous study showed that clinicians do not always agree with the Leeds criteria in determining PA status; instead they assimilate other relevant information e.g. the type of respiratory samples and strain typing results [11].

In response, we have used a consensus method to develop a pragmatic set of criteria for defining chronic PA infection (i.e. the CFHH criteria) which encompasses several components including results of respiratory samples, anti-Pseudomonas IgG antibody levels, VNTR typing/genotyping and clinical context [12]. The diagnostic properties of the CFHH criteria have not been tested. This is the first evaluation of the CFHH criteria, and we compared the CFHH criteria against the Leeds criteria.

METHODS

This is a retrospective cross-sectional analysis of prospectively collected data from adults receiving care at the Sheffield Adult CF Centre throughout 2016. Regulatory approval for this study was obtained from NHS Health Research Authority (IRAS number 210313).

All adults with CF were included, except those with lung transplantation (*n*=7) or on ivacaftor (*n*=13). Lung transplantation alters lung microbiome, which makes the interpretation of PA status difficult [13]. Ivacaftor reduces the likelihood of culturing PA, which may affect the diagnostic properties of the Leeds criteria [14]. Clinical data from 1st January to 31st December 2016 (demographics including social deprivation [15], microbiological results, prescriptions and health outcomes) were extracted from paper notes and electronic patient record, with all data from paper notes reviewed by two investigators to ensure accuracy. Objective adherence data were downloaded from I-neb®, a data-logging nebuliser system. The Leeds criteria [4] were operationalised using an algorithm according to results (PA positive / negative) of cough swab and sputum samples. The multi-component CFHH criteria [12] were operationalised by an investigator with clinical experience in CF (HZH) who reviewed all relevant primary data and the resultant PA status was independently checked by an experienced CF clinician (RC) to ensure accuracy. Further details of the CFHH criteria are provided in Appendix A.

Since the CFHH criteria only categorises PA status as ‘chronic’ and ‘not chronic’ [12], the Leeds criteria categories were also combined into these two groups (i.e. ‘chronic PA infection’ = ‘chronic’; ‘intermittent’, ‘free from infection’ and ‘never’ = ‘not chronic’) for the purpose of analysis. Four analyses were carried out to evaluate the clinical properties of the CFHH criteria. First, the CFHH criteria PA status was cross-tabulated against the Leeds criteria, with agreement in PA status for both criteria calculated using kappa statistics [16]. Second, clinical outcomes (best %FEV_1 i.e. highest %FEV_1 reading obtained in 2016 calculated using the GLI equation [17], %FEV_1 decline from 2015 to 2016, %FEV_1 variability [18], BMI, number of pulmonary exacerbations and days on intravenous antibiotics) were compared between ‘chronic PA infection’ and ‘non chronic PA’ for both criteria using non-parametric methods [19]; as was the proportion of adults on long-term inhaled antibiotics [20]. Third, the likelihood of ‘chronic PA infection’ according to both criteria were compared among the subgroup of adults in which respiratory cultures are less likely to be sensitive (i.e. adults with high adherence to inhaled therapies [21, 22], adults who predominantly provide cough swabs and

adults ≤25 years [11]). Finally, the clinical variables associated with 'chronic PA infection' according to the CFHH criteria were explored.

All analyses were performed using SPSS v25 (IBM Corp) and R v3.5.0 (www.r-project.org). Appropriate descriptive statistics were generated, including effect sizes and confidence intervals. P-values <0.05 were considered statistically significant.

RESULTS

This analysis included 186 adults, with median age of 27 years (IQR 21 to 34 years) and 90 (48.4%) were females. More adults were deemed 'chronic PA' according to the CFHH criteria compared to the Leeds criteria (116, 62.4% vs 79, 42.5%), see Table 1. Where there was disagreement in PA status between the CFHH criteria and the Leeds criteria (37/186, 19.9%), the CFHH criteria diagnosed 'chronic PA' whereas the Leeds criteria diagnosed 'not chronic PA', see Table 2. There was only modest agreement in PA status for both sets of criteria; Cohen's kappa coefficient 0.62, 95% CI 0.51 to 0.72. The demographic and clinical characteristics of the concordant and discordant groups were described in Appendix B.

PA status according to both criteria discriminated the lung health of this cohort, see Table 3. The magnitude of difference was somewhat greater in baseline %FEV_1, %FEV_1 variability, number of exacerbations and intravenous days for the Leeds criteria. However, the converse was true for %FEV_1 decline (–0.6%, 95% CI –1.8 to 0.6% vs –0.2%, 95% CI –1.3 to 1.0%) and BMI (1.8, 95% CI 0.5 to 3.0 vs 1.6, 95% CI 0.4 to 2.8) which somewhat favoured the CFHH criteria. The prescription of long-term inhaled antibiotics also matched the CFHH criteria better, with larger differences between those deemed 'not chronic PA' vs 'chronic PA' compared to the Leeds criteria (–59.7%, 95% CI –70.2 to –46.6% vs –38.5% 95% CI –48.6 to –26.7%). The likelihood of being deemed 'chronic PA' according to the CFHH criteria was less affected by high nebuliser adherence (difference in percentage of 7.1, 95% CI –9.7 to 28.7 vs 8.2, 95% CI –7.7 to 23.4), predominantly cough swabs provided (difference in percentage of 28.4, 95% CI 14.0 to 41.6 vs 48.2, 95% CI 35.6 to 58.2) or younger age (difference in percentage of 20.9, 95% CI 6.2 to 34.6 vs 37.0, 95% CI 23.0 to 48.8), see Table 4.

Of the 116 adults deemed 'chronic PA' according to the CFHH criteria, 77 (66.4%) had positive PA cultures in ≥3 separate calendar months. There were 31 adults (26.7%) who only fulfilled one other minor criterion (see Appendix A for details of the CFHH criteria) and were deemed 'chronic PA' due to being on long-term

inhaled antibiotics, see Table 5. Even if every adult in the centre were on long-term inhaled antibiotics, there would only be additional eight adults deemed ‘chronic PA’. Pseudomonas antibody testing and molecular (variable number tandem repeat, VNTR) typing were only performed in around 40% of the adults who required these tests. The lack of VNTR typing did not affect the diagnosis of chronic PA in this cohort but this diagnosis may have been missed in eight adults due to insufficient Pseudomonas antibody testing.

DISCUSSION

In this analysis, we found that the CFHH criteria diagnosed many more cases of chronic PA infection among adults with CF in comparison to the Leeds criteria – all chronic PA cases according to the Leeds criteria were also chronic with the CFHH criteria but 37/107 (34.6%) of non-chronic PA cases according to the Leeds criteria were diagnosed as chronic PA according to the CFHH criteria. Despite identifying many more cases of chronic PA, the CFHH criteria still retained similar discrimination power for health outcomes among adults with CF. In particular, the difference in FEV_1 decline between non-chronic PA and chronic PA favoured the CFHH criteria, and FEV_1 decline is an important predictor of CF survival [23]. Since there is no perfect reference judge in the diagnosis of chronic PA among adults with CF, the “fair umpire” test [24] could be applied to aid judgments about the value of the CFHH criteria. The principle of this test is to judge the consequence of a new reference test by studying the subgroup with disagreements between the old and new reference tests. Possible umpire tests include exploration of prognosis [24]. The exploratory analyses in Appendix B showed that adults with discordant PA status for both criteria have similar FEV_1 decline compared to adults who were concordant chronic PA. Therefore, a consequence of accepting the CFHH criteria as the reference standard to define PA status among adults with CF is the identification of additional chronic PA cases with similar prognosis to those with “definite” chronic PA i.e. the additional cases are less likely to be merely false-positive results. It could be argued that the shift in diagnosis with the CFHH criteria is desirable because a net benefit may be achieved by identifying those who may otherwise deteriorate without long-term inhaled antibiotics.

Whilst it is important to avoid missing a diagnosis of chronic PA so that efficacious treatments can be initiated, it is nonetheless important to consider the robustness of the diagnosis due to its potential psychological impact [25]. Additional cases diagnosed as chronic PA by the CFHH criteria were mainly picked up among the subgroup of adults in which the Leeds criteria are known to be less sensitive (younger adults and adults predominantly providing cough swabs), which again suggest these are less likely to be

merely false-positive results. Most of the chronic PA diagnosis (79/116, 68.1%) were made according to the major criteria though a sizable minority (31/116, 26.7%) depended on the use of long-term inhaled antibiotics for the diagnosis to be clinched. There is a discretionary element to the prescription of inhaled antibiotics, with variation between centres or even between individual clinicians at the same centre [26]. It is also possible that inhaled antibiotics were prescribed to target lung pathogens other than PA. Nonetheless, the inhaled antibiotics minor criterion does not necessarily render the CFHH criteria vulnerable to false-positive results, since chronic PA can only be diagnosed if there is another evidence to support that diagnosis. Indeed, even if the proportion of adults in Sheffield prescribed long-term inhaled antibiotics were increased from 72% to 100%, only an additional eight cases of chronic PA would be diagnosed with the CFHH criteria.

Perhaps a more important factor to consider is that the CFHH criteria is maximally sensitive if all necessary investigations are performed. All major CF guidelines recommend that respiratory samples should be collected during every clinical review and that clinical reviews should occur at least every three months [27, 28]. In Sheffield, 156/186 (83.9%) of the cohort provided at least four respiratory cultures during 2016. However, the frequency and access to Pseudomonas antibody testing and VNTR typing / genotyping are not specified in current care guidelines. In Sheffield, the aim is to perform Pseudomonas antibody testing during annual reviews among adults without any positive PA culture in the previous year. This was only performed among 46/78 (59.0%) of the adults without positive PA culture throughout 2016. Likewise, VNTR typing could have helped clarify the diagnosis of chronic PA among adults with only one positive PA culture but it was only performed among 10/18 (55.6%) of those adults. As a result, the CFHH criteria may have potentially missed the diagnosis of chronic PA in eight adults. Despite this limitation, we have noted a greater discrepancy between the Leeds criteria and the CFHH criteria (kappa 0.62) in comparison to our previous study which compared the Leeds criteria against clinicians' diagnosis (kappa 0.72 for a 2x2 comparison within the 2015 Sheffield cohort) [11]. This highlights the potential advantages of using a set of objective and standardised criteria to diagnose chronic PA instead of relying on subjective clinician judgement – different clinicians (even those working in the same centre) will have different thresholds in diagnosing chronic PA and there may well be under-detection if clinicians do not all 'sing from the same hymn sheet'.

We acknowledge that our evaluation of the CFHH criteria has several limitations. A single centre study may lack generalisability. The Sheffield cohort is relatively young and centres with older adults are likely to find less discrepancy between the Leeds criteria and the CFHH criteria, since the prevalence of chronic PA infection increases with age, and older adults also tend to have lower FEV_1 and become productive of sputum. Nonetheless, all adults diagnosed with chronic PA according to the Leeds criteria also fulfilled the

CFHH criteria for chronic PA. This suggests that the CFHH criteria match the Leeds criteria but add value by achieving greater sensitivity in younger, healthier adults with minimal sputum and higher FEV_1 where early detection of chronic PA can potentially prevent FEV_1 deterioration, yet the diagnosis can be easily missed. It is likely that the CFHH criteria would still detect more cases of chronic PA in other cohorts. It might be argued that without a true 'gold standard', the only rigorous methodology to evaluate a new test which is more sensitive than an old test is to conduct a randomised trial assessing treatment efficacy in cases detected by the new diagnostic test [29]. However, such test-treatment trials are susceptible to various sources of bias including under-powering and inadequate primary analyses [30]. A large randomised trial to compare the effectiveness of different definitions of chronic PA among people with CF is also unlikely to be feasible due to the number of patients and centres required, and the expense of creating a rigorous detect and treat regimen.

In conclusion, we have demonstrated that the CFHH criteria detected more cases chronic PA yet still retained similar levels of discrimination for health outcomes in comparison to the Leeds criteria. These additional cases were mainly detected in the subgroups in which the Leeds criteria are known to be less sensitive. If all necessary investigations specified in the CFHH criteria were performed, the criteria could have detected even more cases of chronic PA. Our findings provide preliminary evidence that the CFHH criteria is a valid and useful method to diagnose chronic PA among adults with CF. Further evaluation is planned in larger datasets to better understand the diagnostic properties of the CFHH criteria, in particular using the ACtiF dataset (ISRCTN55504164) which is a CF self-management support intervention trial with 608 participants.

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CONFLICT OF INTEREST

None.

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Table 1: Demographic and clinical characteristics of study subjects

	Sheffield dataset[1] (*n* = 186)
Age in years, median (IQR)	27 (21 to 34)
Female, *n* (%)	90 (48.4)
Pancreatic insufficient, *n* (%)	145 (78.0)
CF related diabetes, *n* (%)	54 (29.0)
Social deprivation (IMD quintile[2])	
1 (least deprived), *n* (%)	28 (15.1)
2, *n* (%)	22 (11.8)
3, *n* (%)	40 (21.5)
4, *n* (%)	45 (24.2)
5 (most deprived), *n* (%)	51 (27.4)
Number of relevant microbiological samples	
Cough swabs, median (IQR)	2 (0 to 4)
Sputum samples, median (IQR)	4 (1 to 8)
Total, median (IQR)	7 (4 to 10)
P. aeruginosa status (Leeds criteria)	
Chronic *P. aeruginosa* infection, *n* (%)	79 (42.5)
Intermittent *P. aeruginosa* infection, *n* (%)	29 (15.6)
No *P. aeruginosa*, *n* (%)	78 (41.9)
P. aeruginosa status (CFHH criteria)	
Chronic *P. aeruginosa* infection, *n* (%)	116 (62.4)
Not chronic, *n* (%)	70 (37.6)
Baseline $\%FEV_1$ in 2016, median (IQR)	78.5 (58.5 to 89.6)
$\%FEV_1$ decline from 2015 to 2016[3], median (IQR)	–0.3 (–2.9 to 1.8)
$\%FEV_1$ variability in 2016[4], median (IQR)	4.2 (2.5 to 89.6)
BMI in kg/m^2, median (IQR)	23.2 (20.4 to 26.0)
Number of pulmonary exacerbations, median (IQR)	2 (1 to 3)
Annual IV antibiotic days, median (IQR)	14 (0 to 40)
On long-term inhaled antibiotics, *n* (%)	133 (71.5)

[1] Complete data were available for every clinical variable, except one study subject did not have any FEV_1 readings in 2016 due to inability to perform spirometry testing, 10 study subjects did not have data for FEV_1 decline due to the absence of FEV_1 reading in 2015 and eight study subjects did not have data for FEV_1 variability due to insufficient numbers of FEV_1 readings in 2016.

[2] Social deprivation was calculated as Index of Multiple Deprivation (IMD) scores, which were derived from postcodes using methods previously described [15].

[3] $\%FEV_1$ decline was the absolute change in $\%FEV_1$ from 2015 to 2016 and a negative value implies decline in $\%FEV_1$ (more negative values imply a worse outcome).

[4] $\%FEV_1$ variability was calculated as the median deviation of $\%FEV_1$ using methods previously described [18] (larger values imply a worse outcome).

Table 2: Cross-tabulation of *P. aeruginosa* status according to the CFHH criteria vs Leeds criteria

	CFHH criteria	
	Chronic *P. aeruginosa* infection	Not chronic *P. aeruginosa* infection
The Leeds criteria		
Chronic *P. aeruginosa* infection	79	0
Not chronic *P. aeruginosa* infection	37[1]	70

[1] For a more detailed breakdown, 15/78 (19.2%) of study subjects with no *P. aeruginosa* according to the Leeds criteria were defined as chronic *P. aeruginosa* according to CFHH criteria and 22/29 (75.9%) of study subjects with intermittent *P. aeruginosa* according to the Leeds criteria were defined as chronic *P. aeruginosa* according to CFHH criteria.

Table 3: Health outcomes according to *P. aeruginosa* status, the CFHH criteria vs the Leeds criteria

Health outcomes:	CFHH criteria			Leeds criteria		
	Not chronic (*n* = 70)	Chronic (*n* = 116)	Median of differences between groups[1], (95% CI)	Not chronic (*n* = 107)	Chronic (*n* = 79)	Median of differences between groups[1], (95% CI)
Baseline $\%FEV_1$[2], median (IQR)	87.2 (73.2 to 93.2)	70.4 (49.5 to 83.9)	14.5 (8.7 to 20.8)	84.0 (70.7 to 92.8)	64.9 (43.2 to 81.7)	17.3 (11.1 to 24.1)
$\%FEV_1$ decline from 2015 to 2016[3], median (IQR)	0.0 (–2.6 to 2.4)	–0.5 (–3.3 to 1.5)	–0.6 (–1.8 to 0.6)	–0.2 (–2.6 to 1.9)	–0.5 (–3.3 to 1.6)	–0.2 (–1.3 to 1.0)
$\%FEV_1$ variability in 2016[4], median (IQR)	3.9 (1.5 to 6.2)	4.8 (3.0 to 7.9)	–1.2 (–2.2 to –0.2)	3.9 (2.2 to 6.2)	5.1 (3.3 to 8.9)	–1.5 (–2.5 to –0.5)
BMI, median (IQR)	24.3 (21.2 to 27.3)	22.4 (19.9 to 25.2)	1.8 (0.5 to 3.0)	23.6 (21.2 to 26.8)	21.9 (19.8 to 25.1)	1.6 (0.4 to 2.8)
Number of pulmonary exacerbations, median (IQR)	1 (0 to 2)	3 (1 to 4)	–1.0 (–2.0 to –1.0)	1 (0 to 2)	3 (2 to 5)	–2.0 (–2.0 to –1.0)
IV days, median (IQR)	0 (0 to 14)	28 (12 to 47)	–14 (–26 to –13)	0 (0 to 26)	29 (12 to 59)	–16 (–28 to –14)
On long-term inhaled Abx[5], *n* (%)	24 (34.3)	109 (94.0)	–59.7 (–70.2 to –46.6)[6]	59 (55.1)	74 (93.7)	–38.5 (–48.6 to –26.7)[6]

[1] The between-group differences and confidence intervals for all continuous variables were estimated using a non-parametric method [19]. This method assumes the two groups have the same distribution shifted by a fixed parameter. The shift parameter is not necessarily the difference in median, rather it is the median of all possible differences.

[2] Baseline $\%FEV_1$ was the highest $\%FEV_1$ reading obtained in 2016. % predicted was calculated using the GLI equation [17]. Data were available for 185/186 (99%) of the study subjects.

[3] $\%FEV_1$ decline was the absolute change in $\%FEV_1$ from 2015 to 2016 and a negative value implies decline in $\%FEV_1$ (more negative values imply a worse outcome). Data were available for 176/186 (95%) of the study subjects.

[4] $\%FEV_1$ variability was calculated as the median deviation of $\%FEV_1$ using methods previously described [18] (larger values imply a worse outcome). Data were available for 178/186 (96%) of the study subjects.

[5] Long-term inhaled antibiotic was defined as inhaled antibiotics with intended treatment duration of >3 months. This included eradication treatment for non-tuberculous mycobacteria which is typically two years in duration.

[6] For long-term inhaled antibiotic, the difference in percentages and confidence intervals were displayed. These were calculated using the Wilson procedure without continuity correction [20].

Table 4: The likelihood of chronic *P. aeruginosa* infection according to nebuliser adherence, types of respiratory samples provided and age; the CFHH criteria vs the Leeds criteria

	CFHH criteria			**Leeds criteria**		
	Not chronic (*n* = 70)	Chronic (*n* = 116)	Differences in percentages between groups[1], (95% CI)	Not chronic (*n* = 107)	Chronic (*n* = 79)	Differences in percentages between groups[1], (95% CI)
Normative adherence[2]:	*n* = 23	*n* = 79		*n* = 53	*n* = 49	
Cluster 1 (lowest adherence), *n* (%)	3 (13.0)	15 (19.0)	–5.9 (–19.1 to 14.4)	7 (13.2)	11 (22.4)	–9.2 (–24.2 to 5.7)
Cluster 2, *n* (%)	6 (26.1)	35 (44.3)	–18.2 (–35.6 to 4.7)	18 (34.0)	23 (46.9)	–13.0 (–30.7 to 4.9)
Cluster 3, *n* (%)	8 (34.8)	14 (17.7)	17.1 (–1.7 to 38.5)	15 (28.3)	7 (14.3)	14.0 (–2.1 to 29.1)
Cluster 4 (highest adherence), *n* (%)	**6 (26.1)**	**15 (19.0)**	**7.1 (–9.7 to 28.7)**	**13 (24.5)**	**8 (16.3)**	**8.2 (–7.7 to 23.4)**
Types of respiratory samples[3]:						
Sputum ≥ cough swabs, *n* (%)	32 (45.7)	86 (74.1)	–28.4 (–41.6 to –14.0)	46 (43.0)	72 (91.1)	–48.2 (–58.2 to –35.6)
Cough swabs > sputum, *n* (%)	**38 (54.3)**	**30 (25.9)**	**28.4 (14.0 to 41.6)**	**61 (57.0)**	**7 (8.9)**	**48.2 (35.6 to 58.2)**
Age categories[4]:						
Age >25 years, *n* (%)	30 (42.9)	74 (63.8)	–20.9 (–34.6 to –6.2)	43 (40.2)	61 (77.2)	–37.0 (–48.8 to –23.0)
Age ≤25 years, *n* (%)	**40 (57.1)**	**42 (36.2)**	**20.9 (6.2 to 34.6)**	**64 (59.8)**	**18 (22.8)**	**37.0 (23.0 to 48.8)**

[1] The difference in percentages and confidence intervals were calculated using the Wilson procedure without continuity correction [20].

[2] Objective adherence data from I-neb® were available for 102 study subjects. Normative adherence was calculated then clustered according to previously described methods [21, 22]. The CFHH criteria Chi-square for trend p value = 0.120. The Leeds criteria Chi-square for trend p value = 0.048.

[3] The CFHH criteria Chi-square p value <0.001. The Leeds criteria Chi-square p value <0.001.

[4] The CFHH criteria Chi-square p value = 0.005. The Leeds criteria Chi-square p value <0.001.

Table 5: Further exploration of *P. aeruginosa* status according to the CFHH criteria

How was chronic *P. aeruginosa* infection status (*n* = 116) defined?	
≥3 months with positive samples, *n* (%)	77 (66.4)
1 month or 2 months with positive samples, but on long-term inhaled antibiotics, *n* (%)	21 (18.1)
Pseudomonas antibody +/– VNTR data required, *n* (%)	11 (9.5)
Prior year data required, *n* (%)	7 (6.0)
What was the relative contribution of long-term inhaled antibiotics towards the diagnosis of chronic *P. aeruginosa* status (*n* = 116)?	
Adults who fulfilled either of the major criteria, *n* (%)	79 (68.1)
Adults who fulfilled minor criteria 1 & 3, *n* (%)	5 (4.3)
Adults who fulfilled minor criteria 1 & 4, *n* (%)	1 (0.9)
Adults who relied on long-term inhaled antibiotics to be defined as chronic PA, *n* (%)	31 (26.7)
* Additional number of adults who would have been defined as chronic PA if everyone in the centre were prescribed long-term inhaled antibiotics	8 (out of 70 non chronic PA)
Were all necessary investigations carried out to maximise the sensitivity of the CFHH criteria?	
Pseudomonas antibody testing:	
Adults without any positive culture for *P. aeruginosa* in 2016	78/186 (41.9%)
Adults without positive culture for *P. aeruginosa* and no Pseudomonas antibody	32/78 (41.0%)
Adults without positive culture for *P. aeruginosa* that were deemed 'non chronic PA' according to the CFHH criteria	63
'Non chronic PA' without positive culture for *P. aeruginosa* and did not have Pseudomonas antibody testing	26/63 (41.3%)
* Additional number of adults who would have been defined as chronic PA if those 26 adults without Pseudomonas antibody testing actually had positive antibody	8 (out of 70 non chronic PA)
Pseudomonas molecular (variable number tandem repeat, VNTR) typing:	
Adults with positive culture(s) for *P. aeruginosa* for only one month in 2016	18/186 (9.7%)
Adults with only 1-month positive culture for *P. aeruginosa* and no VNTR typing	8/18 (44.4%)
Adults with only 1-month positive culture for *P. aeruginosa* that were deemed 'non chronic PA' according to the CFHH criteria	5
'Non chronic PA' with only 1-month positive culture for *P. aeruginosa* and did not have VNTR typing	0/5 (0.0%)

Appendix A: A summary of the CFHH criteria to define *P. aeruginosa* status among adults with CF

The full details of the CFHH criteria are outlined in our previous paper [1]. The criteria encompass several components including the number of positive respiratory samples, Pseudomonas antibody levels, molecular (VNTR) typing or genotyping and clinical context (e.g. types of respiratory samples collected and potential reasons for suppressed *Pseudomonas aeruginosa*, PA growth due to treatment factors). There are six criteria statements, two major and four minor. An adult with CF is deemed 'chronic PA' if any of major criteria is fulfilled or if any two of the minor criteria are fulfilled, see Table 1.

Table 1: The six consensus statements to define chronic *P. aeruginosa* infection among adults with CF

'Major criteria' statements (any one finding alone establishes the diagnosis of chronic *P. aeruginosa* infection)

1. ≥3 respiratory samples positive for *P. aeruginosa* in the preceding 1 year, excluding samples collected during a recognised Pseudomonas eradication course (multiple positive samples within the same calendar month can only be counted once).
2. ≥2 respiratory samples at least 3 months apart positive for *P. aeruginosa* in the preceding 1 year, excluding samples collected during a recognised Pseudomonas eradication course, among people who predominantly provide cough swabs (i.e. provide more cough swabs than sputum samples)

'Minor criteria' statements (any two findings are required to establish the diagnosis of chronic *P. aeruginosa* infection)

1. In the preceding 1 year; ≥1 respiratory sample positive for *P. aeruginosa* (excluding respiratory samples collected during a recognised Pseudomonas eradication course) AND / OR a strongly positive (e.g. >5 ELISA unit or >2 OD unit) serum Pseudomonas IgG antibody level, or a trend of rising Pseudomonas IgG antibody levels (excluding serology samples collected during a recognised Pseudomonas eradication course)
2. Insufficient number of respiratory samples positive for *P. aeruginosa* to fulfil the major criteria in a person with CF who is using long-term inhaled anti-pseudomonal antibiotic(s) {inhaled antibiotics prescribed for longer than 3 months are considered 'long-term therapy'}
3. ≥2 respiratory samples at least 6 months apart positive for *P. aeruginosa* of the same type (VNTR typing / genotyping) AND / OR a transmissible *P. aeruginosa* strain (e.g. Liverpool epidemic strain, Manchester epidemic strain or Midlands1 strain)
4. A person who fulfilled the criteria for chronic *P. aeruginosa* infection in the previous year but did not provide adequate number of negative respiratory samples in the current year {That is to say the person did NOT provide any of the following: (a) at least x1 negative BAL sample OR (b) at least x4 negative sputum cultures OR (c) at least x6 negative respiratory samples of any kind, for example this might comprise of x1 negative sputum sample and x5 negative cough swabs. Note that multiple negative samples within the same calendar month can only be counted once and negative samples in a calendar month with any positive sample cannot be counted.}

Major criterion #1 defines chronic PA infection on the basis that frequent sample positivity for PA would indicate chronic infection. It is important that multiple respiratory samples taken within a short time interval (e.g. during an admission for exacerbation) do not bias towards misclassifying intermittent PA infection as chronic, hence multiple positive samples within the same calendar month can only be counted once. Likewise, a positive sample during an eradication course is ignored since it may simply represent intermittent

PA infection that can be subsequently eradicated. The Leeds criteria diagnosed chronic PA if can only be fulfilled if >50% of the months with respiratory samples were positive for PA [2]. Major criterion #1 does not include the proportion component of the Leeds criteria because the chronicity of someone with multiple positive samples (e.g. samples provided monthly and 5/12 were positive) would not be disputed just because other samples were negative.

There will be occasions whereby major criterion #1 is not fulfilled in someone with chronic PA because cough swabs are less sensitive than sputum samples in culturing PA [3,4]. Therefore, major criterion #2 defines chronic PA infection at a slightly lower threshold compared to major criterion #1 (2 months with positive samples instead of 3 months with positive samples) for someone who predominantly provide cough swabs.

The minor criteria are less definitive than the major criteria in diagnosing chronic PA infection and should therefore be triangulated with at least another minor criterion in making the diagnosis.

Minor criterion #1 looks for respiratory samples +/- serology evidence of current PA infection. Pseudomonas serology result only forms part of this minor criterion. Pseudomonas serology result is unnecessary to operationalise the CFHH criteria if a person with CF already has ≥1 positive respiratory samples in the previous 12 months, i.e. serology testing is only required to achieve a diagnosis among those without any positive samples.

Minor criterion #2 considers the fact that a person may have insufficient positive samples to fulfil either of the major criteria if PA growth is suppressed by long-term inhaled anti-pseudomonal antibiotics. The PA growth suppression effect of inhaled anti-pseudomonal antibiotics depends on a multitude of factors and would vary from person to person. Due to the uncertainty regarding how much antibiotics is required to suppress PA growth, an adherence target was not specified for minor criterion #2. It is likely that someone not using inhaled anti-pseudomonal antibiotics for ≥12 months would definitely no longer benefit from any PA suppression effect. It is important to note that all the sample positivity criteria (e.g. major criterion #1, major criterion #2 and minor criterion #1) depend on respiratory samples over the previous 12 months. If someone ceased long-term inhaled anti-pseudomonal antibiotics 3 months previously (e.g. due to completion of a 2-year *M. abscessus* eradication course with amikacin) and only provided a single cough swab sample since the cessation of inhaled antibiotics, that single negative sample certainly does not indicate the absence of PA infection. Therefore, it is specified that a person should cease long-term anti-pseudomonal inhaled antibiotics for ≥12 months in order NOT to fulfil this minor criterion; in that case we can be confident that their

respiratory samples over the preceding 12 months are equally comparable with someone not on inhaled antibiotics.

Minor criterion #3 considers evidence from molecular (VNTR) typing or genotyping of PA positive sample(s). VNTR and genotyping can only be performed if PA is cultured, so it follows that minor criterion #3 cannot be fulfilled in someone without any positive samples. Both identical VNTR type / genotype and transmissible strain are listed within the same minor criterion statement so that it is possible to de-diagnose chronic PA infection. If identical VNTR type / genotype and transmissible strain are listed as separate minor criteria, it would be possible to classify someone as chronically infected with just VNTR testing performed let say 2-3 years ago (note there is no time limit as to when the VNTR testing was performed in the statement). This is undesirable because it would mean classifying someone as chronically infected even if strong evidence of PA eradication emerged later, e.g. negative BAL samples a year after cessation of long-term inhaled antibiotics.

Minor criterion #4 considers the fact that people with high prior probability of being chronically PA infected may well remain chronically infected if there is insufficient evidence of them being free from PA infection. Multiple negative samples in the same calendar month could only be counted once to mirror the sampling interval condition of the major criterion #1. A positive sample within the same calendar month should trump the other negative samples, since standard respiratory cultures are not perfectly sensitive in detecting PA.

If a particular investigation is required to clinch the diagnosis of chronic PA infection but the investigation (e.g. VNTR typing or Pseudomonas serology) was not performed, the CFHH criteria could still be operationalised. In this situation, the particular criterion (e.g. minor criterion #3) would be considered to be absent. For example, in someone who is on long-term inhaled antibiotics and provided x5 negative cough swabs throughout 2016, the absence of Pseudomonas serology means that minor criterion #1 is not fulfilled and that person would not be deemed to have chronic PA infection according to the CFHH criteria.

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Appendix B: Exploring the demographic and clinical characteristics of study subjects with concordant and discordant *P. aeruginosa* status

Table 1: Demographic and clinical characteristics of study subjects according to *P. aeruginosa* status[1]

	Concordant not chronic (*n* = 70)	Discordant, i.e. CFHH criteria chronic, Leeds criteria not chronic (*n* = 37)	Concordant chronic (*n* = 79)
Age in years, median (IQR)	24 (19 to 33)	21 (19 to 28)	30 (26 to 36)
Female, *n* (%)	34 (48.6)	19 (51.4)	43 (54.4)
Pancreatic insufficient, *n* (%)	36 (51.4)	34 (91.9)	75 (94.9)
CF related diabetes, *n* (%)	12 (17.1)	11 (29.7)	31 (39.2)
Social deprivation (IMD quintile[2])			
1 (least deprived), *n* (%)	10 (14.3)	6 (16.2)	12 (15.2)
2, *n* (%)	9 (12.9)	2 (5.4)	11 (13.9)
3, *n* (%)	12 (17.1)	11 (29.7)	17 (21.5)
4, *n* (%)	15 (21.4)	9 (24.3)	21 (26.6)
5 (most deprived), *n* (%)	24 (34.3)	9 (24.3)	18 (22.8)
Number of relevant microbiological samples			
Cough swabs, median (IQR)	3 (1 to 4)	5 (1 to 7)	0 (0 to 2)
Sputum samples, median (IQR)	2 (0 to 5)	1 (0 to 8)	6 (4 to 9)
Total, median (IQR)	5 (4 to 8)	7 (5 to 11)	7 (5 to 10)
Baseline %FEV_1 in 2016, median	87.2 (73.2 to 93.2)	78.6 (62.6 to 91.0)	64.9 (43.2 to 81.7)
%FEV_1 decline from 2015 to 2016[3], median (IQR)	0.0 (–2.6 to 2.4)	–0.6 (–3.1 to 0.5)	–0.5 (–3.3 to 1.6)
%FEV_1 variability in 2016[4], median (IQR)	3.9 (1.5 to 6.2)	3.9 (2.5 to 6.4)	5.1 (3.3 to 8.9)
BMI in kg/m^2, median (IQR)	24.3 (21.2 to 27.3)	23.1 (21.2 to 25.2)	21.9 (19.8 to 25.1)
Number of pulmonary exacerbations, median (IQR)	1 (0 to 2)	1 (1 to 4)	3 (2 to 5)
Annual IV antibiotic days, median (IQR)	0 (0 to 14)	14 (0 to 41)	29 (14 to 59)
On long-term inhaled antibiotics, *n* (%)	24 (34.3)	35 (94.6)	74 (93.7)

[1] Complete data were available for every clinical variable, except one study subject did not have any FEV_1 readings in 2016 due to inability to perform spirometry testing, 10 study subjects did not have data for FEV_1 decline due to the absence of FEV_1 reading in 2015 and eight study subjects did not have data for FEV_1 variability due to insufficient numbers of FEV_1 readings in 2016.

[2] Social deprivation was calculated as Index of Multiple Deprivation (IMD) scores, which were derived from postcodes using methods previously described [1].

[3] %FEV_1 decline was the absolute change in %FEV_1 from 2015 to 2016 and a negative value implies decline in %FEV_1 (more negative values imply a worse outcome).

[4] %FEV_1 variability was calculated as the median deviation of %FEV_1 using methods previously described [2] (larger values imply a worse outcome).

Among the 186 study subjects, 37 adults (19.9%) have discordant PA status whereby the Leeds criteria diagnosed non chronic PA whilst the CFHH criteria diagnosed chronic PA. This 'discordant cohort' was the youngest among all three groups and also provided more cough swabs and fewer sputum samples. These results are consistent with the findings in Table 4 of the main manuscript, which showed that the Leeds criteria were particularly insensitive for diagnosing chronic PA among younger adults and those who predominantly provide cough swabs.

The 'discordant cohort' also had the $\%FEV_1$ decline (median –0.6%, IQR –3.1 to 0.5%) similar to those who were concordant chronic PA (median –0.5%, IQR –3.3 to 1.6%) and greater than those who were concordant non chronic PA (median 0.0%, IQR –2.6 to 2.4%). Since FEV_1 decline is an important predictor of CF survival [3], this finding indicates the potential poor prognosis of the 'discordant cohort'. The 'discordant cohort' may have relatively high baseline $\%FEV_1$ compared to those who were concordant chronic PA (median 78.6%, IQR 62.6 to 91.0% vs median 64.9%, IQR 43.2 to 81.7%), but it must be noted that the 'discordant cohort' were on average 8 years younger (95% CI 5 to 11 years) and FEV_1 declines at a rate of around 1.5%/year among people with CF [4].

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