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BRIEF COMMUNICATION

Pragmatic criteria to define chronic *pseudomonas aeruginosa* infection among adults with cystic fibrosis

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Despite changes in the epidemiology of respiratory bacteriology among adults with cystic fibrosis (CF), *Pseudomonas aeruginosa* remains the most common chronic lung pathogen [1]. *P. aeruginosa* status is important in CF because it influences clinical segregation decisions, choices of preventative inhaled therapy as well as the choice of antibiotics to treat pulmonary exacerbations [2–4]. However, there is currently no "gold standard" to define *P. aeruginosa* status in CF. The Leeds criteria are commonly used in CF research settings [2]. This set of criteria is highly specific in identifying chronic *P. aeruginosa* infection but lack sensitivity when compared against polymerase chain reaction (PCR) techniques, with a tendency to under-diagnose chronic *P. aeruginosa* infection as intermittent infection [5, 6]. Not surprisingly, clinical trials evaluating treatments specifically for adults with chronic *P. aeruginosa* infection generally avoided using the Leeds criteria as part of the eligibility criteria. Instead, a myriad of different definitions are used. For example, the trial evaluating Ciprofloxacin dry powder inhaler used "A positive sputum or throat swab culture for *P. aeruginosa* within the previous 12 months" as one of the eligibility criteria [7], whilst the Aztreonam nebuliser trial used "PA-positive sputum culture within the previous 3 months" [8].

The Leeds criteria were developed in a paediatric population whereby chronic *P. aeruginosa* is not particularly common [9] and *P. aeruginosa* status is still quite fluctuant. A very specific test for chronic *P. aeruginosa* infection, such as the Leeds criteria, works well in a paediatric population. In an

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adult population, chronic *P. aeruginosa* infection becomes much more likely [9] and sensitivity of the chronic *P. aeruginosa* definition becomes increasingly important. Indeed, a previous study found weaker relationships between health outcomes with *P. aeruginosa* status according to the Leeds criteria among adults compared to a paediatric population [10].

In our previous study to understand how clinicians across three specialist adult CF centres in the UK decide on *P. aeruginosa* status [11], there was consistency in decision-making by clinicians across different centres but clinicians did not always agree with the Leeds criteria. Where there was disagreement, clinicians tended to diagnose chronic *P. aeruginosa* infection when the Leeds criteria did not, because clinicians assimilated other relevant information (e.g. proportion of negative cough swabs, information on strain typing) in their decision-making. These results highlight the limitations of the Leeds criteria in defining *P. aeruginosa* status among adults with CF and suggest that a consensus definition for chronic *P. aeruginosa* infection that moves beyond solely depending on standard microbiological results will be useful. Indeed, the challenge of determining *P. aeruginosa* status in CF has clear parallels with the challenge of diagnosing pulmonary exacerbations. Standardised criteria, e.g. the Fuchs' and EPIC criteria may not be a "gold standard" [12, 13], but these criteria nonetheless allow exacerbations to be diagnosed with validity as an endpoint in multi-centre clinical trials. Of note, both the Fuchs' and EPIC criteria consist of a mixture of "objective" (e.g. acute FEV_1 decline) and "subjective" criteria (e.g. change in respiratory symptoms) [12, 13], which again suggests a pragmatic set of chronic *P. aeruginosa* definition should include other relevant clinical information that causes clinicians to disagree with the Leeds criteria.

We therefore built on our previous work by integrating the expertise of clinicians from a greater number of specialist adult centres and using a formal consensus method (nominal group technique [14, 15]) to explicitly develop a pragmatic set of criteria for defining chronic *P. aeruginosa* infection among adults with CF that can be applied clinically and in multi-centre trials. This work was conducted in parallel to the CFHealthHub RCT (ISRCTN55504164), with the intention of using the consensus criteria for this RCT. Clinicians collaborating in the RCT were invited, and ten clinicians across seven adult CF centres in the UK completed all three rounds of the consensus exercise between August and October 2017. The final six consensus statements to define chronic *P. aeruginosa* infection are summarised in Table 1.

This consensus definition of chronic *P. aeruginosa* infection is unique in that it encompasses a number of components including the number of positive respiratory samples, anti- *P. aeruginosa* IgG antibody levels, VNTR typing/genotyping and clinical context (e.g. types of respiratory samples collected and potential reasons for suppressed *P. aeruginosa* growth due to treatment factors). In contrast, currently available criteria for chronic *P. aeruginosa* infection typically only consist of "one component," e.g. the Leeds criteria [2], the European consensus criteria [16] and the UK CF registry definition [17] only consider the proportion/number of positive respiratory cultures. This consensus definition provides a pragmatic and standardised way of using information available in routine clinical practice to achieve a more sensitive diagnosis of chronic *P. aeruginosa* infection among adults with CF. As previously discussed [11], this consensus definition could be utilised to select the appropriate participants for CF clinical trials, help streamline the calculation of "normative adherence" [18] and guide CF management (especially the decision to initiate long-term inhaled antibiotics).

Such a multi-component definition of chronic *P. aeruginosa* infection means that the data collection process

Table 1 The final 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 × 1 negative BAL sample OR (b) at least ×4 negative sputum cultures OR (c) at least × 6 negative respiratory samples of any kind, for example this might comprise of × 1 negative sputum sample and × 5 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.}

to operationalise the definition would be more complex. Data for other investigation results and clinical context must be collected, instead of just collecting data on respiratory samples. The consensus definition does have a clear structure, so the required data collection steps can be summarised in a flow diagram to operationalise the definition with fidelity. An example of such a flow diagram is attached as an online supplement.

The consensus definition is perhaps most sensitive if adequate numbers of respiratory samples are collected, and in settings with a clear pathway for regular testing of anti-*P. aeruginosa* IgG antibody levels and VNTR typing/genotyping. Guidelines from the US, UK and Europe recommend that an adult with CF should be reviewed at least 3-monthly, with respiratory samples collected during each review [19–21]. Current care guidelines do not specify the access and frequency of anti-*P. aeruginosa* IgG antibody levels and VNTR typing/genotyping; hence, these tests may not be universally available. The consensus definition could still be applied without results of anti-*P. aeruginosa* IgG antibody levels and VNTR typing/genotyping, by considering those criteria to be absent.

Additional work is required to further enhance the consensus definition. This consensus exercise involved a relatively small group of clinicians in a single country (although the number of participants is appropriate for the nominal group technique [22]); hence, future research should seek a broader participation in the consensus process, e.g. from other CF health professionals such as microbiologists, and also international opinions. Our ability to successfully complete this exercise over a short time period with minimal resources suggests that similar consensus exercise will be practical in the future. Further consensus exercises would also allow the definition to evolve in response to additional investigational methods that may become routinely available in the future. Data collected during the CFHealthHub RCT could be used to apply, evaluate and subsequently refine the method to operationalise the consensus definition. Other empirical data are also needed to understand the performance of the consensus definition in different settings.

In summary, the proposed consensus definition starts to address a gap in the current methods of diagnosing chronic *P. aeruginosa* infection among adults with CF by using routinely available investigational tools. Future research should attempt to refine the consensus definition by seeking opinion from clinicians outside the CFHealthHub group and using empirical data for evaluation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval for this consensus exercise was obtained from the University of Sheffield School of Health and Related Research (ScHARR) Research Ethics Committee (ScHARR REC reference 015944).

Informed consent Written informed consent was obtained from all participating clinicians prior to the start of this consensus exercise.

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